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Abstract

1. Modelling of Endpoint Postponement for All-Cause Mortality in Statin Trials

Morten Rix Hansen,[1,2] Anton Pottegård,[1] Asbjørn Hróbjartsson,[3] Per Damkier,[1,2] René D Christensen,[3] Kasper Søltoft Larsen,[1] Malene EL Kristensen,[1] Palle M Christensen,[1] Jesper Hallas.[1,2] *[1]Clinical Pharmacology, University of Southern Denmark, Odense, Denmark; [2]Department of Clinical Chemistry and Pharmacology, Odense University Hospital, Odense, Denmark; [3]The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark; [4]Research Unit for General Practice, University of Southern Denmark, Odense, Denmark.*

Background: The average postponement of the outcome event has been proposed as a novel method to present the magnitude of effect for preventive medications. This measure has been shown to have better agreement with patient preferences than conventional outcome measures, including the "number needed to treat" (NNT), possibly because it is more intuitively understood. For some interventions, it may also provide a better theoretical frame for how benefit is distributed among participants than the NNT measure. The aim of this study was to present a novel method for modelling endpoint postponement (EP) from trial data and compare it with the usual approach of measuring the area between survival curves. We also present a formalized meta-analysis of modelled EP for all-cause mortality in statin trials.

Methods: We identified 17 placebo-controlled statin trials that fulfilled our inclusion criteria. Eleven of these presented Kaplan–Meier curves for all-cause mortality. Average EP was calculated as the area between Kaplan–Meier curves by counting pixels on magnified prints for these 11 trials. The modelled EP was computed for all trials on the basis of (1) hazard ratio, relative risk or odds ratio; (2) the cumulative event rate in the untreated group; and (3) the trial's running time. The underlying assumption was that the mortality was reasonably stable within the trials' running time. The modelled EP was subjected to a meta-analysis, using inverse variance weighting in a random effect model.

Results: EPs were generally small for estimates based on pixel-counting, −10 and 27 days for trials both primary and secondary intervention that typically ran over 1.9–6.1 years. The modelled EPs varied between −2 and 34 days. The difference between modeled EP and EP based on pixel-counting was between −8 and 12 days.

The results of the meta-analyses will be presented at the meeting.

Conclusions: Based on these trial data, statin treatment results in a surprisingly small gain in average survival. Our modelled EP estimates agreed reasonably with EPs based on pixel-counting. The modeled EP is amenable to meta-analyses and may be a useful approach to presenting the benefit of preventive treatment.

2. Permanent User Bias in Case–Crossover Studies in Pharmacoepidemiology

Jesper Hallas,[1,2] Shirley V. Wang,[2] Joshua J. Gagne,[2] Sebastian Schneeweiss,[2] Anton Pottegård.[1] *[1]Clinical Pharmacology, University of Southern Denmark, Odense C, Denmark; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.*

Background: In pharmacoepidemiology, the case–crossover design is based on cases that have contrasting drug exposure at the time of an event and at a reference time in the past. If the drug in question should be taken permanently, only certain exposure patterns will occur. These patients cannot be unexposed at the event time and exposed at the reference time, while the opposite pattern can occur if the drug was initiated recently. The resulting odds ratio (OR) would thus be biased upward. As many drugs have a subpopulation of permanent users, this bias might pervade many case–crossover analyses of drug effects.

Objectives: The aims of this study were to demonstrate this "permanent user bias" and to evaluate whether it can be remedied by including a control group (case–time–control design).

Methods: Using nationwide Danish data resources, we conducted case–crossover and case–time–control analyses for combinations of three exposures that are

often intended to be used permanently (statins, insulin, and thyroxin) and three outcomes (retinal detachment, wrist fracture, and ischemic stroke), where the true causal relations were expected to be null. Controls were matched on age, gender, and index date, and exposure was ascertained at 2-month intervals over the preceding 12 months.

Results: For retinal detachment, the case–crossover OR was 1.60 (95% confidence interval (CI): 1.42–1.80) for statins, 1.40 (CI: 1.02–1.92) for thyroxin, and 1.53 (CI: 1.04–2.24) for insulin. Estimates for the control population were nearly identical, leading to near-null case–time–control estimates for the three drug classes. For the wrist fracture and stroke outcomes, case–time–control ORs were consistently above unity (1.09, 1.51, and 1.15 for wrist fracture, and 2.27, 1.87, and 1.67 for stroke), suggesting significant residual bias.

Conclusions: In case–crossover studies of drugs, permanent users confer a moderate bias upward, which is partly remedied by using a control group. Additional research is needed to identify the optimal strategy for selecting this control group.

3. Controlling for Frailty in Cancer Comparative Effectiveness Studies of Older Adults

Jennifer L. Lund, Hanna K. Sanoff, Til Sturmer. *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Older cancer patients often have multiple comorbidities and functional deficits, which likely impact treatment decisions and outcomes. Using databases that lack functional information may lead to biased estimates of real world comparative effectiveness (CE).

Objectives: The aim of this study was to evaluate the impact of controlling for markers of frailty in a CE study of adjuvant chemotherapy for non-metastatic rectal cancer.

Methods: We identified a cohort of 1404 older (65 + years) non-metastatic rectal cancer patients from 2004 to 2009 using the Surveillance, Epidemiology and End Results-Medicare data, who underwent neoadjuvant therapy and surgery and survived 120 days. Using propensity score methods, we evaluated the CE of adjuvant chemotherapy versus observation on mortality, incrementally adding (i) basic confounders (demographics, cancer features, neoadjuvant treatment, comorbidities); (ii) 17 claims-based frailty indicators (e.g., oxygen use, sepsis); and (iii) 30-day post-surgical hospitalization. Among those receiving adjuvant chemotherapy, we evaluated the CE of adjuvant oxaliplatin versus 5-flurouracil (5-FU) on mortality using the same confounder sets. Standardized mortality ratio weighted Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals.

Results: In total, 738 patients (52%) received adjuvant chemotherapy; 52% received oxaliplatin. Overall mortality was 9.8 per 100 person-years (mean follow-up: 3 years). The crude HR for adjuvant chemotherapy versus observation and mortality was 0.68 (0.56, 0.83); after basic confounder adjustment, the estimate was stable (aHR = 0.68 (0.54, 0.85)). Adjustment for frailty markers attenuated the aHR (0.71 (0.56, 0.90)), and inclusion of post-surgical hospitalization led to further attenuation (aHR = 0.75 (0.59, 0.95)). Among patients receiving adjuvant chemotherapy, the crude HR comparing oxaliplatin versus 5-FU on mortality was 1.0 (0.72, 1.39); adjustment for basic confounders and additional frailty markers produced similar results.

Conclusions: Our results suggest that adjustment for markers of frailty and post-surgical hospitalization may improve the validity of cancer CE studies using non-active comparators.

4. Impact of Violations of the Assumptions of the Self-controlled Case Series Design in Pharmacoepidemiological Studies: An Example of Antidepressants Use and the Risk of Hip Fracture

Md Jamal Uddin,[1] Rolf H. H. Groenwold,[2] Mohammed Sanni Ali,[2] Gianmario Candore,[3] Mark C. H. de Groot,[4] Patrick C. Souverein,[4] Yolanda Alvarez,[3] Svetlana V. Belitser,[4] Arno W. Hoes,[2] Anthonius de Boer,[4] Kit C. B. Roes,[2] Olaf H. Klungel,[4] Helga Gardarsdottir.[4] *[1]Department of Statistics (Epidemiology and Biostatistics), Shahjalal University of Science and Technology, Sylhet, Bangladesh; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [3]European Medicines Agency, EMA, London, UK; [4]Division of Pharmacoepidemiology and Clinical Pharmacology, University of Utrecht, Utrecht, The Netherlands.*

Background: The self-controlled case-series (SCCS) design has been applied to control for time-fixed (un)

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measured confounding in pharmacoepidemiological studies. Although previous studies acknowledged that violations of the key SCCS assumptions lead to biased exposure effects, little is known about the impact of the violations in empirical studies.

Objectives: The aim of this study was to evaluate the impact of various levels of violation of assumptions of the SCCS design and different definitions of observation/risk periods in a study of antidepressants use and the risk of hip/femur fracture (HF).

Methods: Information on adults with an HF who used antidepressants at any time during the observation period 2001–2009 was extracted from the UK THIN (6632 cases) and the Dutch Mondriaan (136 cases) databases. The incidence rate ratio (IRR) using this design was defined as the rate of events during exposed periods and during all other observed periods. The IRR of HF was estimated using conditional Poisson regression.

Results: The IRRs appeared extremely biased when all subjects were censored at their first/last HF or when the analysis was restricted to subjects experiencing hip fracture after initiating antidepressant use. For example, in THIN, IRRs for >365 days of exposure were 1.26 [1.13–1.42] when complete follow-up was considered and 40.1 [32.2–49.9] when censoring was at the first event. However, modest censoring at the first or last event (up to 20%) had a minor impact on the IRRs. Additionally, results were consistent when including subjects who were exposed at the start of follow-up and for different risk period definitions.

Conclusions: The SCCS design is sensitive to violations of the assumptions and yields apparently biased estimates when a significant number of subjects are censored at the event or when the analysis is restricted subjects who experienced hip fracture after initiating antidepressants. The performance of this design may differ across studies and across databases. Therefore, in each SCCS study, correct specification of the SCCS design should be carefully assessed and reported.

5. Probabilistic Multiple-Bias Analyses of Observational Studies on Narcolepsy Following Vaccination with GlaxoSmithKline's Inactivated Adjuvanted (AS03) A/H1N1pdm09 Pandemic Influenza Vaccine

Kaatje Bollaerts,[1] Vivek Shinde,[2] Gaël Dos Santos,[3] Germano Ferreira,[4] Vincent Bauchau,[4] Catherine Cohet,[4] Thomas Verstraeten.[1] *[1]P95 Pharmacovigilance and Epidemiology Services, Leuven, Belgium; [2]GlaxoSmith Kline Vaccines, Philadelphia, PA, USA; [3]Business & Decision Life Sciences, Brussels, Belgium; [4]Glaxo SmithKline Vaccines, Wavre, Belgium.*

Background: An increase in the incidence of narcolepsy was first observed in Finland and Sweden towards the end of the 2009 H1N1 influenza pandemic. Preliminary epidemiological studies suggested a temporal association with GlaxoSmithKline's (GSK) Dresden-manufactured A/H1N1pdm09 vaccine, leading to a number of additional studies across Europe. Given the public health urgency to investigate the signal, these studies used readily available retrospective data from various sources. The potential for bias in such settings was generally acknowledged. Although several health authorities advocate quantifying the potential impact of biases, this was not systematically carried out in any of the narcolepsy studies.

Objectives: The aim of this study was to quantify the impact of a cascade of potential bias and confounding on the association between GSK's A/H1N1pdm09 vaccine and narcolepsy.

Methods: We apply bias-level multiple-bias analyses to two published studies on the association of the vaccine with narcolepsy: a paediatric cohort study from Finland and a case–control study from France. In particular, we developed Monte Carlo simulation models based on formal models of bias and confounding to evaluate a potential cascade of biases, including confounding by indication and natural H1N1 influenza infection, selection bias, and disease and exposure misclassification. All bias parameters were evidence based to the extent possible.

Results: Given the assumptions made and when accounting for all potential sources of bias, the rate ratio of 13.78 (95%CI: 5.72, 28.11) in the Finnish study was reduced to 4.88 (2.5th to 97.5th percentile: 1.91, 10.84) and the odds ratio of 5.43 (95%CI: 2.6, 10.08) in the French study to 1.93 (2.5th to 97.5th percentile: 0.78, 4.04).

Conclusions: The observed association between GSK's A/H1N1pdm09 vaccine and narcolepsy persists in a multiple-bias sensitivity analysis in the Finnish study but not in the French study. We advocate the use of multiple-bias analyses to better understand the robustness of study findings, and to increase accuracy of data used to inform subsequent benefit-risk decision.

6. Confounding by Drug Formulary Restrictions in Pharmacoepidemiologic Research

Kristian B. Filion, Maria Eberg, Pierre Ernst. Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada.

Background: The potential consequences of confounding owing to drug formulary restrictions in pharmacoepidemiologic research remain incompletely understood.

Objectives: The aim of this study was to illustrate this potential bias using the example of fluticasone/salmeterol combination therapy (Advair©), an oral inhaler used for the treatment of asthma and chronic obstructive pulmonary disease, whose use is restricted in the province of Quebec, Canada.

Methods: We identified all new users of fluticasone/salmeterol in Quebec's administrative health databases and classified those who received their initial dispensation of fluticasone/salmeterol between 1 September 1999 and 30 September 2003 as users from the liberal use period and those who received their initial dispensation between 1 January 2004 and 31 October 2006 as users from the restricted period. The primary outcome was time to first hospitalization for respiratory causes within 12 months of cohort entry.

Results: Our cohort included 77 212 new users of fluticasone/salmeterol, 72 154 from the liberal period and 5058 from the restricted period. Compared with the liberal period (crude rate per 100 person-years = 18.7, 95% confidence interval [CI] = 18.3, 18.9), the restricted period (crude rate = 26.2 events per 100 person-years, 95%CI = 24.7, 27.9) was associated with an increased rate of hospitalization for respiratory causes (crude hazards ratio [HR] = 1.41, 95% = 1.32, 1.51). Subsequent adjustment for age, sex, and hospitalization for respiratory causes in the previous year attenuated the association (HR = 1.05, 95% CI = 0.98, 1.12). Further adjustment for comorbidities, respiratory and non-respiratory medications, prescribing physician specialty, and season resulted in a significantly lower rate during the restricted period (HR = 0.78, 95%CI = 0.73, 0.83).

Conclusions: Drug formulary restrictions can result in substantial and unexpected confounding and should be considered during the design and analysis of pharmacoepidemiologic studies.

7. Perioperative Beta-Blocker (BB) Therapy in Non-cardiac Surgery and the Risk of In-hospital Myocardial Infarction (MI), Stroke, and Mortality

Elisabetta Patorno,[1] Robert Glynn,[1] Sebastian Schneeweiss,[1] Jun Liu[1], and Brian Bateman.[1,2] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA.*

Background: Based on two small randomized controlled trials (RCTs) from the 1990s, beta-blockers (BBs) were promoted to prevent perioperative cardiac events in non-cardiac surgery. In 2008, a large RCT (POISE trial) showed decreased myocardial infarction (MI) risk associated with perioperative BB initiation, but an increased risk of stroke and mortality. Subsequent observational studies have produced mixed results.

Objectives: The aim of this study was to evaluate the risk of in-hospital MI, stroke, and mortality associated with perioperative BB initiation in patients undergoing elective non-cardiac surgery.

Methods: From a large US commercial healthcare database, we identified patients ≥18 years who underwent moderate- to high-risk elective non-cardiac surgery between 2004 and 2013 (index surgery), had a surgical visit within a 60-day window prior to surgery (to ensure potential access to treatment), and had no BB use in the 180 days prior to that window. Among those, we identified BB initiators and non-initiators within 60 days of surgery. A 1:1 propensity score (PS) matching was used to balance over 90 baseline characteristics. Relative risks (RR) and 95% confidence intervals (CIs) for MI, stroke (either ischemic or hemorrhagic), and mortality events occurring during the index surgery hospitalization were calculated using logistic regression models.

Results: Of 245 257 patients undergoing surgery, 7548 initiated a BB (3.1%). The risk of in-hospital MI, stroke, and mortality was 0.30%, 0.46%, and 0.23% among BB initiators, and 0.11%, 0.11%, and 0.12% in non-initiators. Among 14 884 1:1 PS-matched patients, there were 21 (0.28%) MIs among BB initiators versus 25 (0.34%) among non-initiators (RR = 0.84, 95% CI = 0.47–1.50), along with 32 (0.43%) versus 18

(0.24%) strokes (RR = 1.78, 1.00–3.18), and 17 (0.23%) versus 12 (0.16%) deaths (RR = 1.42, 0.68–2.97). Sensitivity analyses based on 1:3 fixed ratio PS-matching yielded consistent results.

Conclusions: These preliminary results suggest perioperative BB initiation may be associated with an increased risk of stroke in patients undergoing non-cardiac surgery in routine care, mirroring what was observed in the POISE trial. Further research on how such an effect may vary across individual BB agents and dose is warranted.

8. Evidence of Potential Unmeasured Confounding in a Comparison of Cardioselective β-Blockers and Non-dihydropyridine Calcium Channel Blockers in Patients with Acute Coronary Syndromes and Chronic Obstructive Pulmonary Disease: Results of a Multi-national Study

Yaa-Hui Dong,[1] Matthew Alcusky,[2] Vittorio Maio,[2] Jun Liu,[1] Mengdan Liu,[2] Li-Chiu Wu,[3] Chia-Hsuin Chang,[3,4] Mei-Shu Lai,[3,4] Joshua J. Gagne.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Jefferson School of Population Health, Thomas Jefferson University, Philadelphia, PA, USA; [3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.*

Background: Despite reluctance to prescribe β-blockers (BBs) to chronic obstructive pulmonary disease (COPD) patients owing to concerns about acute bronchospasm, some observational studies suggest that BBs reduce mortality in COPD patients. However, these studies have important limitations, such as focusing on prevalent users and a lack of active comparator groups.

Objectives: The aims of this study were to examine the effectiveness of BBs in patients with acute coronary syndromes (ACS) and COPD with a propensity score (PS)-matched, active comparator, new-user cohort design and to assess potential unmeasured confounding by examining a short-term COPD hospitalization outcome.

Methods: We identified patients with ACS and COPD starting a cardioselective BB or a non-dihydropyridine calcium channel blocker in three US claims databases, the Italy Regione Emilia-Romagna Database, and the Taiwan National Health Insurance Database. Outcomes were mortality, CV hospitalizations, and COPD hospitalizations. We used stratified Cox regression models to estimate HRs and 95%CIs for each outcome and in each database after variable-ratio matching on site-specific PSs. We used random-effects meta-analyses to combine HRs across databases.

Results: A total of 16 995 patients were eligible, of whom 4591 died, 3045 had CV hospitalizations, and 868 had COPD hospitalizations. Cardioselective BBs were not associated with reduced risk of mortality (HR 0.90, 95% CI 0.75–1.09) or CV hospitalizations (HR 1.01, 95%CI 0.85–1.21) but were inversely associated with COPD hospitalizations (HR 0.52, 95%CI 0.45–0.61). The HR for COPD hospitalizations restricted to the first 30 days of follow-up was 0.51 (95%CI 0.32–0.82).

Conclusions: This multi-national study found a strong inverse association between cardioselective BBs use and COPD hospitalizations, even in the first 30 days of follow-up, suggestive of severe confounding. The persistence of this bias and the potential for it to affect the mortality and CV hospitalization outcomes call into question the results of prior studies.

9. Outcomes of Carotid Artery Stenting (CAS) in Older Patients with Carotid Stenosis

Jessica J. Jalbert,[1,2] Louis L. Nguyen,[3] Marie D. Gerhard-Herman,[4] Michael R. Jaff,[5] Christopher J. White,[6] Andrew T. Rothman,[1] John D. Seeger,[1] Hiraku Kumamaru,[1] Lauren A. Williams,[1] Chih-Ying Chen,[1] Jun Liu,[1] Herbert D. Aronow,[7] Joseph A. Johnston,[8] Thomas G. Brott,[9] and Soko Setoguchi.[10] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA; [2]LA-SER Analytica, New York, NY, USA; [3]Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Boston, MA, USA; [4]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [5]Division of Cardiovascular Medicine, Massachusetts General Hospital, Boston, MA, USA; [6]Ochsner Clinic Foundation, New Orleans, LA, USA; [7]Cardiac Catheterization Laboratory, St. Joseph Mercy Hospital, Ypsilanti, MI, USA; [8]Eli Lilly and Company, Indianapolis, IN, USA; [9]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA; [10]Duke Clinical Research Institute, Durham, NC, USA.*

Background: Outcomes during and after the periprocedural period (PPP) among Medicare beneficiaries

undergoing carotid artery stenting (CAS) have not been described, despite increasing CAS dissemination.

Objectives: The aims of this study were to describe outcomes during and after the PPP among Medicare patients undergoing CAS and to evaluate how patient and provider characteristics affect outcomes.

Methods: We linked 2000–2009 Medicare data to the Carotid Artery Stenting Database (2005–2009), which contain basic clinical information on patients undergoing CAS in Medicaid- and Medicare-certified facilities. Medicare patients aged ≥66 years were followed up from the CAS date for death and stroke/transient ischemic attack (TIA) during and after the PPP (30 days post-procedure). Using Kaplan–Meier estimators, we derived risks overall and among patient subgroups defined by demographics, clinical, and center-level factors. To evaluate how outcome risks differed across subgroups, we used Cox regression while accounting for clustering.

Results: Among 22 516 CAS Medicare patients, mean age was 76.3 years, 60.5% were male, 93.8% were White, 91.2% were high-surgical risk, and 47.4% were symptomatic. Crude 30-day mortality and stroke/TIA risks were 1.7% (95% confidence interval (CI): 1.5–1.8%) and 3.3% (95%CI: 3.0–3.5%), respectively. Age ≥80 years, symptomatic carotid stenosis, and non-elective hospitalizations were associated with increased adjusted hazards of mortality and stroke/TIA during and after the PPP. Presence of a stroke center, government ownership, and ≥500 beds were associated with increased adjusted hazards of peri-procedural mortality and stroke/TIA. Mortality over a mean follow-up time of 2 years was 32.0% (95%CI: 31.0–33.0%) and differed by subgroup, 27.7% (95%CI: 26.4–28.9%) for asymptomatic patients, 37.3% (95%CI: 35.8–38.7) for symptomatic patients, and 41.5% (95%CI: 39.7–43.3) for patients ≥80 years of age.

Conclusions: While peri-procedural risks for CAS approximated those recommended in clinical guidelines, mortality was high, possibly negating expected benefits of CAS. Future research should identify factors predicting which Medicare patients have a hazard of mortality low enough to justify CAS, particularly in patients who are symptomatic and ≥80 years old.

10. Effects of Clopidogrel and Proton Pump Inhibitors on Cardiovascular Events in Patients with Type 2 Diabetes Mellitus After Drug-Eluting Stent Implantation: A Nationwide Cohort Study

Chi-Feng Hsieh,[1] Weng-Foung Huang,[1] Yi-Ting Chiang,[1] and Chun-Yen Chen.[2] [1]*Institute of Health and Welfare Policy, National Yang-Ming University, Taipei, Taiwan;* [2]*Mackay Medical College, New Taipei City, Taiwan.*

Objectives: The aim of this study was to investigate whether there is an increased risk of cardiac events in diabetic patients with a combined therapy of clopidogrel (CLO) and proton pump inhibitors (PPIs) after drug-eluting stent (DES) deployment.

Methods: By using National Health Insurance Research Database, all patients undergoing DES (limus-eluting stents [LESs] and paclitaxel-eluting stents [PESs]) deployment who received 90 days of CLO with or without PPI therapy were enrolled. Endpoints were acute coronary syndrome (ACS) and readmission for revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery) after 3, 6, and 12 months.

Results: A total of 6603 diabetic patients received LESs (5933 in the CLO subgroup and 670 in the CLO plus PPIs subgroup), and 3202 patients received PESs (2923 in the CLO subgroup and 279 in the CLO plus PPIs subgroup). The patients who received CLO plus PPIs were at higher risk of myocardial infarction (MI) than those receiving CLO within 1 year after DES deployment (LESs: 6-month hazard ratio [HR] = 1.63, 95% confidence interval [CI], 1.25–2.14 and 1-year HR = 1.37, 95%CI, 1.09–1.71; PESs: 3-month HR = 1.72, 95%CI, 1.02–2.89). Patients with a history of MI who received CLO plus PPIs were at higher risk of ACS after LES implantation (HR = 1.55; 95%CI, 1.11–2.16) than those in the CLO group. Similar results were not found for PESs.

Conclusions: In "real-world" diabetic patients with LES deployment, the combination of PPIs and CLO is associated with higher rates of ACS after 6 months and 1 year. Even after correction for confounding factors, concomitant PPI use remained an independent predictor of cardiac events, emphasizing the clinical importance of this drug–drug interaction.

11. Cardiovascular Safety and Effectiveness of Glucagon-like Peptide-1 Receptor Agonists (GLP-1-RAs) in Routine Care

Elisabetta Patorno,[1] Brendan Everett,[2] Allison Goldfine,[3] Robert Glynn,[1] Jun Liu,[1] Seoyoung Kim.[1,4] [1]*Division of Pharmacoepidemiology and Pharmacoeconomics,*

Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [3]Clinical Research, Joslin Diabetes Center, Boston, MA, USA; [4]Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital, Boston, MA, USA.

Background: Evidence from small, randomized trials suggests that glucagon-like peptide-1 receptor agonists (GLP-1-RAs) may reduce cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). The few observational studies available have produced mixed results.

Objectives: The aim of this study was to evaluate whether GLP-1-RAs, when added to metformin, reduce the risk of major adverse cardiovascular events (MACE) compared with the addition of other antidiabetic agents to metformin in routine care.

Methods: Within a large commercial US health insurance database, we identified T2DM patients who intensified metformin with new use of GLP-1-RAs, second-generation sulfonylureas (SUs), DPP-4 inhibitors (DPP-4is), or insulin between 2005 and 2013. Propensity score (PS) matched analyses (1:1 ratio) were used to balance more than 100 baseline characteristics and evaluate the risk of MACE (i.e., a hospitalization for acute coronary syndrome, stroke, or cardiac revascularization) in three separate PS-matched cohorts (GLP-1-RAs vs. SUs, vs. DPP-4is, and vs. insulin). Follow-up started on the day following intensification and ended at a MACE event, insurance disenrollment, or the end of a 365-day period.

Results: After PS matching, we identified 28 182 new users for GLP-1-RAs versus SUs with 138 and 151 MACE events, respectively (incidence rates = 12.2/1000 person years (py) and 13.6/1000 py); 35 526 new users for GLP-1-RAs versus DPP-4is with 209 and 194 events (14.6/1000 py and 13.5/1000 py); and 47 458 new users for GLP-1-RAs versus insulin with 306 and 409 events (16.0/1000 py and 22.2/1000 py). The hazard ratio (95% confidence interval) for MACE was 0.90 (0.71–1.13) for initiators of GLP-1-RAs versus SUs, 1.08 (0.89–1.31) versus DPP-4is, and 0.72 (0.62–0.84) versus insulin. The decreased risk versus insulin disappeared in a sensitivity analysis restricted to patients with baseline HbA1c level available and including this value in the PS model (HR = 0.95, 0.69–1.32).

Conclusions: In this large nationwide investigation, the addition of GLP-1-RAs to metformin was not associated with a reduced risk of MACE when compared with the addition of other antidiabetic agents. More research is needed to define whether specific subgroups of patients with T2DM may benefit from the use of GLP-1-RAs.

12. The Risk of Developing Ménière's Disease in Association with Use of Antiarrhythmic Drugs

Nadja A. Stohler,[1,2] Saskia G. Bruderer,[1,2] Daniel Bodmer,[3] Susan Jick,[4] and Christoph R. Meier.[1,2,4]
[1]Department of Pharmaceutical Sciences, Basel Pharmacoepidemiology Unit, Division of clinical Pharmacy and Epidemiology, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Department of Biomedicine and Clinic for Otorhinolaryngology, University Hospital Basel, Basel, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Boston University, School of Medicine, Lexington, MA, USA.

Background: Ménière's disease (MD) is a disease of the inner ear with a poorly understood pathophysiology. The inner ear is compartmentalized and filled with two different fluids, which are separated by membrane barriers: potassium-rich and sodium-poor endolymph on one side, and sodium-poor and potassium-rich perilymph on the other side. Amongst others, K^+ and Na^+ channels help maintain the ion gradient between the two liquids. Class I and III antiarrhythmic drugs act via Na^+ or K^+ channels, respectively, and may therefore influence these gradients.

Objectives: The aim of this study was to analyse the association between antiarrhythmics (class I and III) interacting with Na^+ and K^+ channels and the risk of developing MD.

Methods: We performed a case–control analysis using data from the UK-based Clinical Practice Research Datalink. Between 1993 and 2013, we identified case patients between 18 and 79 years with an incident MD diagnosis and matched four MD-free control subjects to each case. The controls were selected according to the criteria of identical age, sex, number of years of active history in the database prior the index date, and general practice. We stratified exposure by timing of the last prescription prior to the index date (current <180 days, past ≥ 180 days), and by duration of use. We calculated odds ratios (OR) with 95% confidence intervals (CIs) using conditional logistic regression and adjusting for potential confounders.

Results: Of 7777 cases with incident MD, 66% were female with an overall mean age of 56.7 years (±SD 13.7) at first MD diagnosis. Among these cases and 31 108 matched controls, current use of Na^+ channel blocking antiarrhythmics was associated with an OR of 1.92 (95%CI 1.10–3.36), while no association was found between current use of K^+ channel blockers and the risk of developing incident MD (OR 1.12, 95%CI 0.81–1.55). These analyses were adjusted for body mass index, smoking, and alcohol consumption.

Conclusions: Our findings suggest that patients who use class I antiarrhythmics acting on Na^+ channels, but not class III antiarrhythmics acting on K^+ channels, may be at a slightly increased risk of developing MD.

13. Patterns of Antihyperglycemic Drug Use and Effect on Implementation of a New-User Active Comparator Study

Mugdha N. Gokhale, John B. Buse, M. Alison Marquis, and Til Sturmer. *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: New-user active comparator studies often use data combined from multiple years, which could be an issue if there are changes in treatment initiation patterns during the study period. In recent years, second-line treatment of type 2 diabetes with dipeptidyl peptidase-4 inhibitors (DPP) increased while thiazolidinediones (TZD) decreased.

Objectives: We examined the patterns of initiation of antihyperglycemic drugs and their effect on the implementation of a new-user study comparing DPP versus TZD using combined data from all years.

Methods: Using Medicare claims from 2008 to 2012, we identified initiators of second-line treatment with DPP, TZD, or sulfonylureas (SU) (100%) after a 6-month washout and classified them based on year of initiation. We examined whether the prevalence of baseline variables within DPP and TZD initiators changed based on year of initiation. Second, we assessed whether the determinants of initiating DPP versus TZD changed over time. This was carried out by comparing the odds ratio (OR) and 95%CI for DPP versus TZD for all baseline variables for each year.

Results: During the study period, the proportion of DPP initiators increased from 11.7% ($n=2637$) to 30.1% ($n=5024$), while TZD initiators decreased from 19.7% ($n=3989$) to 2.6% ($n=429$) with a clear crossing of curves around 2010. The proportion of SU initiators remained constant around 70%. There were negligible differences in the baseline characteristics within initiators of DPP and TZD across years (<5%). The odds ratios for DPP versus TZD changed very slightly across years even for key variables like baseline diabetes complications (OR 1.2 (1.0–1.3) in 2008; 1.3 (1.1–1.6) in 2012) and metformin use (OR 1.3 (1.2–1.4) in 2008; 1.5 (1.2–1.8) in 2012).

Conclusions: Over the study period, the initiation of DPP increased while TZD initiation decreased. No changes in the baseline characteristics of DPP and TZD initiators combined evince that the indication did not change over time. The determinants to prescribe DPP versus TZD for each year did not change, implying that the market dynamics have little implications for confounding control while comparing DPP versus TZD with a new-user design using combined data from all years.

14. Metformin Use in Patients with Renal Impairment: A Drug Utilization Study in Denmark and the United Kingdom

Christian F. Christiansen,[1] Vera Ehrenstein,[1] Stine Skovbo,[1] Helene Nørrelund,[1] Henrik T. Sørensen,[1] Lin Li,[2] and Susan Jick.[2] [1]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark;* [2]*Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA.*

Background: According to current recommendations, metformin is contraindicated in patients with severe renal impairment and should be used with caution in patients with mild to moderate renal impairment.

Objectives: The aims of this study were to estimate prevalence of renal impairment in metformin users and to examine utilization of metformin among diabetes patients with renal impairment.

Methods: We conducted this two-country drug utilization study using the Aarhus University Prescription Database, the Laboratory Information System, and the Danish National Patient Registry including data from Northern Denmark and the Clinical Practice Research Datalink from the UK for years 2000 to 2011. We included patients aged ≥30 years with

medically treated diabetes. Using cross-sectional analysis, we described patient demographics, comorbidities, and co-medications according to metformin use and renal function, using estimated glomerular filtration rates (eGFR). We also examined changes in metformin use within 90 days after first decline in eGFR after study start.

Results: We included 172 052 diabetes patients in Denmark and the UK. Users of metformin were overall younger and had a lower prevalence of comorbidities and metformin contraindications including renal impairment than users of other antidiabetic drugs. Prevalence of eGFR <60 ml/min/1.73 m^2 among new metformin users was 11.0% in Denmark and 25.2% in the UK. In contrast, eGFR values <45 ml/min/1.73 m^2 were less prevalent (2.7% of new metformin users in Denmark and 4.9% in the UK). Most metformin users continued taking the medication after the first decline in eGFR. No more than 45% of patients discontinued metformin even after an eGFR drop below 30 ml/min/1.73 m^2. There was no clinically significant dose reduction with decreasing eGFR level discernible from the data.

Conclusions: Mild to moderate renal impairment was common among metformin users, most of whom continued metformin after developing severe renal impairment—against current recommendations.

15. Channeling of Linagliptin to Patients with Renal or Hepatic Impairment

Chandrasekar Gopalakrishnan,[1] Elisabetta Patorno,[1] Olesya I. Zorina,[2] Sebastian Schneeweiss,[1] Dorothee B. Bartels,[2] Jun Liu,[1] and John D. Seeger.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Corporate Department of Global Epidemiology, Boehringer Ingelheim GmbH, Ingelheim, Germany.*

Background: Prescribing of medications may be selective with respect to factors that could influence effectiveness or tolerability. Linagliptin (LINA) is a dipeptidyl peptidase-4 inhibitor (DPP-4i) recently approved in the USA for treatment of type 2 diabetes mellitus (T2DM). LINA is the only diabetes medication whose labeling does not require dose adjustment in patients with renal or hepatic impairment, and this could translate into preferential prescribing of LINA to such patients.

Objectives: We sought to assess the extent of channeling of LINA and whether this channeling matches expectations arising from the labeling.

Methods: Within a large, nationwide US health insurance database (Optum Clinformatics), T2DM patients who initiated LINA or other non-insulin glucose lowering agents between May 2011 and June 2012 were described in terms of medical characteristics at time of initiation.

Results: Of 155 345 T2DM patients who initiated a non-insulin diabetes agent, 2820 (1.8%) did so with LINA. The prevalence of baseline kidney disease among patients initiating LINA (11.9%) was higher than initiators of other DPP-4i (6.5%), sulfonylureas (6.9%), glitazones (6.8%) or metformin (3.9%), with only meglitinide initiators (14.2%) having a higher prevalence. Although rare, patients initiating LINA tended to have a slightly higher prevalence of baseline chronic liver disease (3.0%) than other DPP-4i (2.6%), metformin (2.5%), sulfonylurea (2.9%) and glitazones (2.6%). These conditions and further comorbidities translated into higher average Charlson comorbidity scores among LINA (1.68) initiators compared with other DPP-4i (1.43), metformin (1.27), sulfonylureas (1.44) and glitazones (1.37), with only meglitinide initiators having a higher score (1.79) than LINA. These patterns were also observed in another US insurance claims database (MarketScan).

Conclusions: Patients initiating LINA exhibit a higher burden of comorbidities, including renal and hepatic disease, which reflect labeling and need to be accounted for in comparative effectiveness or safety studies of LINA.

16. Effectiveness of Intensification Therapy in Patients with Type 2 Diabetes Who Used Basal Insulin Only

Reimar W. Thomsen,[1] Lisbeth M. Baggesen,[1] Mette Søgaard,[1] Lars Pedersen,[1] Helene Nørrelund,[1] Esben S. Buhl,[2] Christiane L. Haase,[2] and Søren P. Johnsen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Novo Nordisk Scandinavia AB, Copenhagen, Denmark.*

Background: Limited data exist on the glycemic benefit of different intensification therapies in type 2 diabetes (T2D) patients who use basal insulin only in a routine clinical setting.

Objectives: The aim of this study was to examine the effect of different intensification therapies on glycemic control among T2D patients who received basal insulin only therapy.

Methods: We identified a cohort of all individuals with a first basal insulin only prescription in Northern Denmark, 2000–2012, and identified all add-on intensification therapy with bolus insulin, premixed insulin, or GLP-1 receptor agonists. We used Poisson regression to compute adjusted relative risks (aRRs) of reaching an HbA1c target value of <7.0% adjusted for age, gender, comorbidities, and baseline HbA1c.

Results: We included 6114 patients with a first basal insulin prescription and HbA1c measurements. Of these 2156 (35.3%) who received intensification therapy after a median of 11 months, 59.2% ($n=1276$) were intensified with premixed insulin, 27.5% ($n=592$) with bolus insulin, and 11.8% ($n=255$) with GLP-1 agonists, and only 1.5% ($n=33$) received more than one add-on regimen simultaneously. Overall, 25.9% attained an HbA1c target of <7% within 3–6 months after intensification. Reductions in median HbA1c were 0.9 percentage points (pp) for premixed insulin, 0.4 pp for bolus insulin, 0.9 pp for GLP-1 agonists, and 1.1 pp for patients with >1 intensification drug. Compared with the large group of premixed insulin intensification as reference, aRRs of attaining an HbA1c <7% were 1.01 (95%CI 0.84–1.21) for bolus insulin and 1.28 (95%CI 1.02–1.60) for GLP-1 agonists.

Conclusions: In this population-based study, one-fourth of T2D patients reached a target HbA1c <7% within 3–6 months after intensification of their basal insulin only therapy. GLP-1 agonists were associated with higher target attainment than premixed insulin intensification.

17. Statin Initiation in the Context of Diabetes Risk

Robert J. Glynn, and Paul M. Ridker. *Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA.*

Background: Statins reduce cardiovascular risk in many types of patients but can also increase risk of being diagnosed with diabetes. Simple prediction models for incident type 2 diabetes have excellent performance characteristics, but it is unclear whether they can identify patients at particular risk at the time of statin initiation.

Objectives: We evaluated the predictive performance of a Framingham risk score for diabetes (PW Wilson *et al.*; Arch Intern Med 2007) in a multi-cultural statin trial population and tested whether risk of diabetes on statin therapy was modified across levels of this score.

Methods: The double-blind JUPITER trial randomized 17 603 men and women without prior cardiovascular disease or diabetes to daily rosuvastatin 20 mg or placebo and followed them up for up to 5 years for the primary endpoint of a first confirmed cardiovascular event and the secondary endpoint of physician-reported diabetes.

Results: The externally derived diabetes risk score performed well: separately in those randomized to rosuvastatin and placebo, the score had excellent discrimination (C-statistic ≥ 0.83) and acceptable calibration (Hosmer–Lemeshow $p > 0.05$) with rates of newly diagnosed diabetes ranging from below 0.2/100 person-years (p-yrs) among those in the bottom score quartile to above 3.0/100 p-yrs in the top quartile. Based on 406 cases of newly diagnosed diabetes during follow-up, those assigned to active rosuvastatin had a 29% increased rate relative to placebo, adjusted for predicted risk (relative risk 1.29; 95% confidence interval (CI): 1.06–1.57) with no evidence for heterogeneity across risk categories on this scale (homogeneity $p=0.67$). However, on the rate difference scale, heterogeneity was apparent (homogeneity $p=0.033$) with no meaningfully higher rate of newly diagnosed diabetes in those assigned to active rosuvastatin if they had a below median baseline risk score (risk difference (RD) 0.04; 95%CI: −0.09 to 0.17 cases/100 p-yrs) but a significantly increased rate with rosuvastatin in those with above-median baseline risk (RD 0.52; 95%CI: 0.10 to 0.94 cases/100 p-yrs).

Conclusions: A clinical diabetes risk score can partition patients at the time of statin initiation into some with low risk and others with higher risk of newly diagnosed diabetes during treatment.

18. Impact of Adherence to Oral Antidiabetics on All-Cause Mortality: A Population-Based Study

Patrice Simard,[1] Nancy Presse,[1] Louise Roy,[2] Marc Dorais,[3] Brian White-Guay,[1] Agnès Rakel,[2] and Sylvie Perreault.[1] [1]*Faculté de Pharmacie, Université*

de Montréal, Montreal, QC, Canada; [2]Centre Hospitalier de l'Université de Montréal, Hôpital Saint-Luc, Montreal, QC, Canada; [3]StatSciences Inc, Notre-Dame de l'Ile-Perrot, QC, Canada.

Background: Oral antidiabetics (OAD) have been shown to reduce the risk of mortality, particularly among metformin users, which had risk reductions of 36% for cardiovascular-related death and 33–40% for all-cause mortality. However, very few studies have assessed adherence to OAD and all-cause mortality.

Objectives: A population-based nested case–control study design was used to investigate the relationship between adherence to OAD and all-cause mortality among incident users of OAD.

Methods: Incident OAD users were identified using healthcare databases of residents covered by the public drug insurance plan of the Province of Quebec, Canada. Patients initiated OAD therapy between 2000 and 2009 and were aged 45–85 years at cohort entry. A nested case–control design was conducted to study mortality occurrence. Each case was matched to 10 controls by gender, age and duration of follow-up. The adherence to OAD was measured by calculating the medication possession ratio. Conditional logistic regression models were used to estimate the association between adherence to OAD and all-cause mortality adjusting for various potential confounders.

Results: The cohort included 63 859 incident OAD users at entry: mean age was 68 years, 45% were male, 37% had coronary artery disease, 82% had hypertension, and 62% had dyslipidemia. Most patients initiated their OAD treatment with biguanides (78%) and sulfonylureas (12%). The average follow-up time was 48 months. Among those deemed adherent, the risk of mortality was decreased compared with non-adherent (rate ratio: 0.67 [95%CI 0.64–0.70]). The likelihood for mortality was higher for patients with heart failure (1.56 [1.49–1.65]), ≥2 cardiovascular diseases (1.45 [1.39–1.52]), amputations (2.03 [1.42–2.91]), chronic viral infections (1.73 [1.44–2.07]), corticosteroid use (1.69 [1.56–1.89]), and ≥1 hospital admissions (1.73 [1.65–1.80]). Conversely, mortality was least likely for patients with dyslipidemia (0.76 [0.73–0.79]) and hypertension (0.88 [0.83–0.94]).

Conclusions: Adherence to OAD seems to be associated with a risk reduction of mortality. Further research is needed to confirm this risk. Residual confounding may remain a potential issue.

19. Impact of Assisted Reproductive Therapy (ART) on Infant Health and Mortality

Katherine Jane Sullivan, Allison Schroeder, David Tabano, and Neel Vaidya. *Center for Pharmaceutical Outcomes Research, University of Colorado Anschutz Medical Campus, Skaggs School of Pharmacy, Aurora, CO, USA.*

Background: Use of assisted reproductive therapy (ART) for conception nearly doubled from 1999 to 2008 and continues to increase. Literature evaluating outcomes from ART including birth weight and overall newborn survival is limited; although in-depth information on ART as a whole is available, there is no Colorado-specific data on neonatal intensive care unit (NICU) admission rates or mortality following ART.

Objectives: The aims of this study were (i) to quantify NICU admission risk to infants conceived via ART compared with non-ART and (ii) to compare mortality rates within the first year of life between ART NICU infants and non-ART NICU infants.

Methods: Using data from the Colorado Department of Public Health and Environment, Colorado Birth Certificate Database from 2007 to 2012, a retrospective cohort study using multivariable logistic regression was performed. Rates of NICU admission in ART and non-ART infants were determined, then 1-year mortality rates in ART NICU infants and non-ART NICU infants were compared. Separate analyses were performed on singleton-only births. Non-hospital delivery, delivery prior to 22 weeks' gestation, discharge and readmission to NICU, and missing data were excluded. All mothers were between the ages of 25 and 45 years, were non-smokers, and had a live birth.

Results: A total of 190 795 live births in 2007–2012 were included into the birth cohort for analysis (12 666 ART births; 178 129 non-ART births). ART births had a 52% increased risk of being admitted to the NICU compared with non-ART births (OR 1.52 [95%CI 1.38, 1.69]); singleton-only ART births had a 39% greater risk of being admitted to the NICU compared with singleton non-ART births (OR 1.39 [95%CI 1.18, 1.65]). The risk of mortality within 1 year after birth among the ART NICU admissions is 46.7% lower compared with non-ART NICU admissions; however, it was not a statistically significant difference (OR 0.533 [95%CI 0.283, 1.002]).

Conclusions: ART births in Colorado have a higher risk of NICU admission compared with non-ART births. Although ART increases NICU admission risk, mortality risk within 1 year of birth among ART births admitted to the NICU was not statistically different from non-ART births.

20. Safety of Seasonal Influenza Vaccines in Pregnancy: VAMPSS Update

Christina D. Chambers,[1,2] Carol Louik,[3] Kenneth L. Jones,[1] Allen A. Mitchell,[3] and Michael Schatz.[4,5] *[1]Department of Pediatrics, University of California San Diego, La Jolla, CA, USA; [2]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA; [3]Slone Epidemiology Center, Boston University, Boston, MA, USA; [4]Department of Allergy and Immunology, Kaiser Permanente, San Diego, CA, USA; [5]American Academy of Allergy, Asthma and Immunology, Milwaukee, WI, USA.*

Background: Annual variations in seasonal influenza vaccines require that their pregnancy safety be monitored.

Objectives: The aim of this study was to evaluate the fetal safety of influenza vaccines available in the USA in years following the pandemic H1N1 season.

Methods: The Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) continued to monitor risks for birth defects and other adverse pregnancy outcomes in women who received seasonal influenza vaccine in pregnancy. The cohort arm of VAMPSS conducted by the OTIS Collaborative Research Group prospectively followed pregnant women in the USA or Canada who did or did not receive seasonal influenza vaccine in any trimester. In parallel, the case–control arm of VAMPSS conducted by the Slone Epidemiology Center Birth Defects Study interviewed mothers of malformed cases and controls from five US regions about influenza vaccination during pregnancy.

Results: The VAMPSS cohort arm completed follow-up of 1205 vaccinated and 448 unvaccinated women between 2010 and 2014. The relative risk (RR) for major birth defects overall in first-trimester vaccine-exposed compared with unexposed approximated 1.0 (RR 1.23, 95% confidence interval (CI) 0.60, 2.50); no increases were noted within seasons. Rates of spontaneous abortion, preterm delivery, and small for gestational age infants were also similar between groups. The VAMPSS case–control arm completed maternal interviews for 4118 cases with specific malformations and 2084 non-malformed controls in the 2011/2012 or 2012/2013 seasons. For 41 specific defects evaluated in either season or both seasons combined, adjusted odds ratios approximated 1.0; only one lower bound of the 95%CI exceeded 1.0. Twenty eight of the 41 specific defects met the VAMPSS criteria of no evidence of risk (upper bound 95%CI < 4.0).

Conclusions: Continued surveillance of each seasonal formulation of influenza vaccine received by pregnant women (regardless of trimester) provides reassurance that these vaccines were not associated with increased risks for adverse pregnancy outcomes.

21. Otic Quinolones After Tympanostomy Tubes Associated with Persistent Tympanic Membrane Perforations

Adel A. Alrwisan,[1] Almut G. Winterstein,[2] and Patrick J. Antonelli.[3] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [3]Department of Otolaryngology, University of Florida, Gainesville, FL, USA.*

Background: Systemic quinolones have been linked to collagen disorders (e.g., tendon rupture). Otic quinolone administration exposes the tympanic membrane to higher concentrations, but no study has examined the effect on tympanic membrane perforation (TMPs).

Objectives: We thought to investigate whether otic quinolones with or without corticosteroids carry an additional risk of TMP compared with otic neomycin plus hydrocortisone (HC) preparations.

Methods: This retrospective cohort study utilized administrative claims data of children eligible for Medicaid services in 29 states between 1999 and 2006. Children entered the cohort after placement of tympanostomy tubes (TTs) and dispensing of quinolone or neomycin + HC eardrops. Children were followed up 24 months after their first eardrop prescription. We defined persistent TMP as the need for tympanoplasty. A Cox regression model adjusted for age, sex, race, adenoidectomy, and TT reinsertion was used to compare the rate of TMP between quinolone and neomycin + HC exposed children.

Results: A total of 96 595 children had a risk of 19 and 14 TMPs/10 000 patient-years for quinolones and neomycin + HC, respectively. Patients exposed to quinolones had a higher risk of TMP with an adjusted hazard ratio of 1.92 (95% confidence interval (CI) 1.31–2.8). Stratified by quinolone, the hazard ratios were 1.79 (95%CI 1.21–2.65) for ofloxacin, 2.17 (95%CI 1.39–3.37) for ciprofloxacin + HC, and 2.58 (95%CI 1.51–4.42) for ciprofloxacin + dexamethasone.

Conclusions: In children with TTs, exposure to otic quinolones is associated with increased risk of persistent TMPs. Eardrops with quinolones and corticosteroids may pose a greater risk of persistent TMPs. This risk must be balanced against the risk of hearing loss with otic neomycin use.

22. Immunization Status at Discharge from the Neonatal Intensive Care Unit (NICU)

Sudha R. Raman,[1] Stephen D. DeMeo,[2] Christoph P. Hornik,[1] Reese Clark,[3] and P. Brian Smith.[1] *[1]Duke Clinical Research Institute, Duke University, Durham, NC, USA; [2]Department of Pediatrics, Duke University Medical Center, Durham, NC, USA; [3]Pediatrix-Obstetrix Center for Research and Education, Sunrise, FL, USA.*

Background: Underimmunization at discharge from the neonatal intensive care unit (NICU) can persist into early childhood, putting vulnerable infants at risk of vaccine preventable diseases. Few studies have assessed immunization status of infants at NICU discharge.

Objectives: The aim of this study was to assess the immunization status of infants >60 days of age at time of discharge from the NICU and assess for trends in vaccination status over time.

Methods: We conducted a multicenter retrospective cohort study using electronic medical record data from 322 US NICUs managed by the Pediatrix Medical Group. The cohort included infants discharged home between 2007 and 2012, who had been in the NICU continuously from day of life 0 to 60, excluding those diagnosed with any immunodeficiency. The infants were grouped by age at discharge (2 months: 60–119 days; 4 months: 120–179 days; 6 months: 180–365 days). We assessed whether infants were immunized with five vaccine types [diphtheria/tetanus/acellular pertussis (DTaP), inactivated polio virus (IPV), *Haemophilus influenza* B (HiB), pneumococcal conjugate vaccine 7-valent/13-valent, hepatitis B (HepB)]. The outcome was the proportion of infants who were up to date (UTD) at discharge, defined as at least one dose of each vaccine type for the 2-month group, two doses for the 4-month group, and three doses for the 6-month group [except HepB (two doses) and HiB (two doses if started with DTaP/IPV/HepB combination vaccine)].

Results: Of 24,599 infants in the cohort, 80% of the 2-month group (17 251/21 673), 39% (1010/2582) of the 4-month group, and 26% (78/304) of the 6-month group were UTD, with only 4% of all infants being completely unimmunized at discharge ($n = 1101$). Having UTD status was most common for HepB in the three groups (97%, 51%, and 79% in the 2-, 4-, and 6-month group, respectively). UTD status at discharge was higher in 2012 versus 2007 for all groups (2 months: 85% vs. 75%; 4 months: 45% vs. 32%; 6 months: 29% vs. 12%).

Conclusions: Many infants are underimmunized at NICU discharge, especially if discharged after 4 months. Up-to-date immunization status has improved over time. The influence of infant clinical characteristics on vaccination status should be examined.

23. Evaluation of a Composite Endpoint for Measuring Neonatal Benefit in Clinical Trials of Tocolytics Using Electronic Medical Records (EMRs)

Jeanne M. Pimenta,[1] Emma Brinkley,[2] Kathleen J. Beach,[3] Timothy H. Montague,[4] and Christina D. Mack.[2] *[1]Worldwide Epidemiology, GlaxoSmithKline, Uxbridge, Middlesex, UK; [2]Epidemiology, Real-World and Late Phase Research, Quintiles, Research Triangle Park, NC, USA; [3]Maternal Neonatal Health Unit, GlaxoSmithKline, Research Triangle Park, NC, USA; [4]Clinical Statistics, GlaxoSmithKline, Philadelphia, PA, USA.*

Background: Neonatal benefit resulting from prolongation of pregnancy is a required endpoint in randomized controlled trials (RCTs) of new tocolytics. We previously defined a composite endpoint (CE) of neonatal mortality and morbidity combining outcomes of death, respiratory distress syndrome (RDS), bronchopulmonary dysplasia, intraventricular hemorrhage grade 3/4, periventricular leukomalacia, necrotizing enterocolitis + surgery, treated retinopathy of prematurity (ROP), sepsis and meningitis. Initially,

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the CE rate was assessed using data from one 3° referral center (Medical University of South Carolina (MUSC)) and was used to determine RCT sample size.

Objectives: The aim of this study was to understand if the CE rate was representative across the USA. We compared results with a diverse population from four integrated data networks.

Methods: Retrospective analyses were conducted using mother–infant linked pairs in electronic medical records from seven US States in Quintiles' COMparative effectiveness PAtient Safety and Surveillance (COMPASS) Network (2001–2012), funded by GSK. As in MUSC, the frequency of the CE was assessed among singleton infants born ≥24 weeks' gestational age (w GA); those with congenital conditions or born to women with eclampsia/HELLP, placental conditions, or infection were excluded.

Results: Comparing uncomplicated, singleton births in COMPASS ($n = 56\,572$) and MUSC (17 957), preterm birth rates (<37w GA) were 4.7% and 8.3%, respectively; 2.3% and 3.4% had one or more of the morbidities in the CE. In MUSC, the CE was 96–100% among 24–29w GA infants; rates were 20–30% lower in COMPASS, declining steadily from 89 to 78%. CE rates remained lower in week 30 in COMPASS (78% vs. 51%) but merged by week 31 and remained similar for later GA births. Differences in the CE during 24–30 weeks reflect lower continuous positive airway pressure/ventilator use in RDS and laser treatment in ROP cases in COMPASS.

Conclusions: Exact comparisons between populations are challenging owing to differences in distribution of race, geography, hospital type/size, and medical coding and treatment protocols. As a result of lower CE rates among early preterms, an adaptive study design allowing sample size re-estimation was implemented for planned RCTs.

24. Validity of Delivery Outcomes Within the Medicaid Analytic eXtract (MAX) Database

Caitlin A. Knox,[1,2] Juan Hincapie Castillo,[1] and Almut G. Winterstein.[1,3] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Safety and Epidemiology, HealthCore, Andover, MA, USA; [3]Department of Epidemiology, University of Florida, Gainesville, FL, USA.*

Background: Previous research has developed and validated algorithms to identify premature birth utilizing both maternal and infant information in administrative claims data. However, research regarding the identification of delivery outcomes utilizing only maternal claims is limited.

Objectives: The aim of this study was to assess the validity of delivery outcomes including the identification of cesarean section delivery, as well as premature deliveries in the Medicaid Analytic eXtract (MAX) database.

Methods: We identified women aged 12 to 55 years with a claim for a live birth using the 1999–2006 Florida and Texas MAX data. ICD9-CM codes were used to ascertain potential cases in the MAX claims, and then we reviewed the corresponding BCR for each subject. We calculated sensitivity, specificity, and positive predictive value (PPV) using the BCR as reference.

Results: We identified 67 937 live births in MAX for women with 12 months' continuous eligibility before the start of pregnancy until delivery. After linkage with the BCR, among the 6760 births identified as premature in MAX, the sensitivity was 46.0%, with specificity of 97.0% and a PPV of 72.8%. Utilizing CPT-4 procedure codes, ICD-9-CM diagnosis codes, we identified almost 13 000 live births that occurred via cesarean section delivery in MAX with a sensitivity of 54.3%, a specificity of 99.5%, and a PPV of 98.1%.

Conclusions: We were able to conduct an objective evaluation of the validity of diagnostic codes used to identify delivery outcomes. Algorithms for both premature and cesarean section delivery using only maternal administrative claims produced moderate and high specificity, respectively. Our results can be used to conduct corrections of measurement error in epidemiologic studies dealing with pregnancy and related outcomes.

25. Using Pharmacoepidemiologic Studies to Inform Drug Policy

Sandra Knowles,[1,3] Mina Tadrous,[1,2,3] Diana Martins,[2] Tara Gomes,[1,2,3] David Juurlink,[2,3,4] and Muhammad Mamdani.[1,2,3] *[1]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]University of Toronto, Toronto, ON, Canada;*

[4]*Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Background: Pharmacoepidemiologic studies generate information regarding drug utilization, benefits and risks, which can be incorporated into drug class reviews to provide important contextualization to help inform public drug policy. The Ontario Drug Policy Research Network framework for drug class reviews combines multiple types of evidence to generate policy recommendations for the Ontario government. Within this model, pharmacoepidemiology studies have been used as a tool to quantify and describe the use, adherence and safety of medications within a drug class.

Objectives: We describe the role of pharmacoepidemiology research in formulary modernization for the Ontario Public Drug Programs using two drug class reviews.

Methods: Using linked databases in Ontario including prescription records and physicians' claims data, studies are conducted for health resource utilization, adherence and patient characteristics. Public drug program prescription records for six other provinces are also analyzed. National and provincial trends on all retail prescriptions are captured through IMS Geographic Prescription Monitor.

Results: In the review of triptans for migraines, a potential safety issue was identified based on Ontario utilization data; approximately 10% of triptan users were considered at risk for medication overuse headache. This led to policy recommendations that included expanded availability of triptans but with monthly quantity limits. A review of testosterone replacement therapy (TRT) showed a 29-fold increase in use of topical TRT over 7 years in men 65 years and older. Approximately one-third of new testosterone users had no lab test for testosterone levels in the year prior to their first prescription for TRT, despite current policy stipulating that baseline testing be carried out. These data, in conjunction with safety concerns and questionable efficacy of TRT in older men, resulted in more restrictive policy recommendations for TRT.

Conclusions: Pharmacoepidemiologic studies provide essential information regarding drug utilization, benefits and risks; these data have been incorporated into our comprehensive drug class reviews to help inform public drug policy.

26. Impact of Texas's 2010 "Pill Mill" Law on Opioid Prescribing and Utilization

Tatyana Lyapustina,[1,2] Lainie Rutkow,[3] Matthew Daubresse,[1,4] and Caleb Alexander.[1,4,5] [1]*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA;* [2]*Johns Hopkins School of Medicine, Baltimore, MD, USA;* [3]*Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA;* [4]*Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA;* [5]*Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, USA.*

Background: One of the ways that states address the abuse and diversion of prescription opioid pain relievers is through strengthening the regulation of pain management clinics; however, the effect of such measures remains unclear.

Objectives: The aim of this study was to quantify the impact of Texas's 2010 "pill mill" law on overall and high risk opioid prescribing and utilization.

Methods: We used the IMS Health LRx LifeLink database to examine anonymized, patient-level pharmacy claims for a closed cohort of individuals filling prescription opioids in Texas between September 2009 and August 2011. Our primary outcomes were derived at a monthly level and included average morphine equivalent dose (MED) per transaction, opioid volume, number of opioid prescriptions, and quantity of opioids dispensed. We compared observed values among our cohort with the counterfactual, which we estimated based on pre-intervention levels and trends. We conducted sensitivity analyses by varying the length of the observation period and examining an open rather than closed cohort.

Results: Our final cohort included 8.3 million patients, 737 123 providers, and 2829 pharmacies. During the 24-month observation period, there were 724 million prescription transactions in Texas, of which 10.5% were for opioids. Overall, Texas's "pill mill" law was associated with declines in average MED (0.57 mg/month, 95% confidence interval (CI) 0.057–1.09), monthly opioid volume (9.99 kg/month, 95%CI 7.11–12.86), monthly number of opioid prescriptions (12 200 prescriptions/month, 95%CI 9150–15 300), and monthly quantity of opioids dispensed (714 000 pills/month, 95%CI 550 000–877 000). These reductions were

concentrated among prescribers and patients with the highest opioid prescribing and utilization at baseline. Sensitivity analyses supported the findings of the main results.

Conclusions: Following the implementation of Texas's 2010 "pill mill" law, there were moderate, statistically significant reductions in average MED, opioid volume, number of opioid prescriptions, and quantity of opioids dispensed within the state. These reductions were limited to individuals with higher risk baseline behaviors.

27. Risk of Major Adverse Cardiovascular Events and Transfusion Among US Hemodialysis Patients After CMS and FDA Policy Changes in 2011

Cunlin Wang,[1] Robert Kane,[1] Mark Levenson,[1] Jeffrey Kelman,[2] Mickel Wernecke,[3] Joo-Yeon Lee,[1] Chris Worrall,[2] Thomas MaCurdy,[3] and David J. Graham.[1] *[1]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [2]Center for Medicare and Medicaid Service, Baltimore, MD, USA; [3]ACUMEN, LLC, Burlingame, CA, USA.*

Background: In 2011, the Centers for Medicare and Medicaid Services (CMS) changed its reimbursement policy for erythropoiesis stimulating agents (ESA) used in dialysis. Additionally, the Food and Drug Administration revised the prescribing information for ESAs to reduce their use. Effects of these changes are not yet fully understood.

Objectives: The aim of this study was to compare the risk of major adverse cardiovascular events (MACE) and blood transfusions in dialysis patients before and after the policy changes.

Methods: Patients from the CMS End Stage Renal Disease Program were divided retrospectively into two cohorts based on the date of dialysis initiation and were followed up until the first occurrence of renal transplantation, Medicare disenrollment, switch to peritoneal dialysis, or a study outcome. The window for the pre-policy cohort was January 2008 to December 2009, and for the post-policy cohort, July 2011 to June 2013. Cox regression was used to estimate the relative risk between the two periods for all study outcomes: MACE and its components (acute myocardial infarction (AMI), stroke, and all-cause mortality), hospitalized congestive heart failure (CHF), venous thromboembolism (VTE), and transfusion episodes.

Results: A total of 69 718 incident dialysis patients were included in the analysis. Baseline characteristics at the dialysis initiation were similar between cohorts. Decreases in both the percentage of patients receiving ESAs and the average ESA dose were observed after the policy changes, independent of patients' hemoglobin levels. Post-policy, the risk of stroke decreased (hazard ratio (HR) = 0.77, 95% confidence interval (CI) 0.64–0.93) among patients initiating dialysis. The risk of MACE, death, CHF, and VTE was similar between cohorts, and the risk of AMI was slightly lower in the post-policy cohort: HR = 0.89, 95%CI 0.77–1.02, $p < 0.1$. Blood transfusions increased post-policy (HR = 1.09, 95%CI 1.07–1.12) but trended toward equilibrium at the end of 2-year follow-up.

Conclusions: Post-policy, there was a significant reduction in the risk of stroke, no change in the risk of MACE, and a slight decrease in the risk of AMI, while transfusion use increased. Additional analysis is needed to confirm whether the risk of transfusion regressed to pre-policy level over time.

28. The Effect of Medicaid Peer Review Prior Authorization Policies on Pediatric Use of Antipsychotic Medications

Mehmet Burcu,[1] Julie M. Zito,[1] Stephen McKean,[2] Rob Warnock,[2] Peter Herbert,[2] Sumit Verma,[2] Chris M. Worrall,[3] Steve Chu,[3] and Ali Mohamadi.[4] *[1]Pharmaceutical Health Services Research, University of Maryland Baltimore, Baltimore, MD, USA; [2]Acumen, LLC, Burlingame, CA, USA; [3]Centers for Medicare and Medicaid Services, Washington, DC, USA; [4]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA.*

Background: Several state Medicaid agencies have recently adopted novel approaches targeting expanded use of atypical antipsychotic (AAP) medications in children, namely peer review prior authorization (PA) policies. Physicians are required to receive pre-approval from these Medicaid agencies through contracted clinicians (peer reviewers) to be able to prescribe AAPs to children under a certain age.

Objectives: The aim of this study was to assess the impact of peer review PA policies on the use of AAPs and other psychotropic medication classes among Medicaid-insured youth (0–17 years).

Methods: We used administrative Medicaid claims data from four geographically diverse states. PA policies were

implemented for children ages <5 years in state A, <6 years in states B and C, and <8 years in state D. We used interrupted time-series design to assess monthly use of AAPs and other psychotropic medication classes across 36 months. In multivariable logistic regression models with generalized estimating equations, we added interaction terms for time period and age group to assess whether changes in medication use differed by age group in the post-policy versus pre-policy periods.

Results: Compared with the pre-policy period, AAP use in the post-policy period decreased significantly for children ages <5–8 years in state A from 0.06% to 0.04% (adjusted odds ratio (OR) = 0.65 [0.53–0.79]), in state B from 0.13% to 0.08% (OR = 0.71 [0.64–0.77]), in state C from 0.15% to 0.14% (OR = 0.91 [0.85–0.98]), and in state D from 0.35% to 0.26% (OR = 0.75 [0.72–0.78]). In contrast, AAP use increased significantly for older youth in states B, C, and D, except for those in state A (OR = 0.93 [0.91–0.96]). Restrictions on AAP use did not result in increased use of other psychotropic medication classes, which mostly remained stable or declined.

Conclusions: With the implementation of peer review PA policies, the use of AAP medications declined substantially in children younger than 5–8 years, with no apparent substitution of other psychotropic medication classes. The policy had no discernible effect in older youth whose AAP use continues to be high. Long-term consequences of these policies on clinical outcomes warrant further research.

29. Education and Presence of an Infectious Diseases (ID) Pharmacist in an Outpatient Primary Care Clinic

Diane M. Gomes,[1,2] Aisling R. Caffrey,[1,2] and Kerry L. LaPlante.[1,2] *[1]Infectious Diseases Research Program, Providence Veteran Affairs Medical Center, Providence, RI, USA; [2]College of Pharmacy, University of Rhode Island, Kingston, RI, USA.*

Background: In the USA, antibiotics are the second most commonly prescribed medications in ambulatory settings. Preventing unnecessary antibiotic use in the primary care setting is essential to overall stewardship efforts.

Objectives: The aim of this study was to assess the change in antibiotic prescribing for outpatient infections after implementation of education and infectious diseases (ID) pharmacist presence in a primary care clinic.

Methods: The Providence VA Medical Center consists of eight primary care teams. In March 2014, two teams with medical residents received the following intervention: presence of an ID pharmacist during clinic hours and live education on prescribing guidelines for outpatient infections (e.g., sinusitis, bronchitis). The other six teams served as the control group. Primary care visits for infections, identified from diagnosis codes, were extracted for the pre-intervention (March to September 2013) and post-intervention (March to September 2014) periods. We then identified antibiotic prescriptions 1 day prior to the visit or within 3 days after the visit. Between-group differences were assessed using X^2, Fisher exact, or Cochran–Mantel–Haenszel.

Results: There were 350 primary care visits associated with an infection diagnosis of interest during the pre ($n = 137$) and post ($n = 213$) periods among the intervention primary care teams. There were no significant differences in total number of diagnoses or antibiotic prescriptions between the pre and post periods in this group. The percent of visits with antibiotics prescribed decreased for bronchitis (32% to 27%) and pneumonia (67% to 36%) and increased for sinusitis (40% to 71%) and skin and soft tissue infections (32% to 46%). These changes were non-significant. In the post period, there were 872 primary care visits and 76% were with control primary care teams. The intervention group prescribed less antibiotics than the control group for bronchitis (27% vs. 71%, $p < 0.001$) and upper respiratory tract infections (URTIs) (19% vs. 60%, $p < 0.001$) in the post-intervention period.

Conclusions: Antibiotic prescribing for bronchitis and URTIs was significantly lower among primary care intervention teams, with access to an ID pharmacist and education, as compared with the control teams.

30. Trends in Enterobacteriaceae Resistance in the Veterans Affairs (VA) New England Healthcare System

Haley J. Morrill,[1,2,3] Aisling R. Caffrey,[1,2,3] Lan Jiang,[3] David M. Dosa,[3] and Kerry L. LaPlante.[1,2,3] *[1]Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA; [2]College of Pharmacy, University of Rhode Island, Kingston, RI, USA; [3]COIN-LTSS, Providence Veterans Affairs Medical Center, Providence, RI, USA.*

Background: The emergence and spread of antimicrobial resistance in Enterobacteriaceae is a serious global public health concern of increasing magnitude.

Objectives: The aim of this study was to quantify changes in antimicrobial resistance in Enterobacteriaceae among the acute care hospitals of the VA New England Healthcare System.

Methods: We included all positive microbiology *Escherichia coli* and *Klebsiella pneumoniae* cultures collected during a hospital admission from the following sites: blood, urine, lower respiratory, and cerebrospinal fluid (sites selected per National Healthcare Safety Network recommendations). Resistance rates were assessed over a 10-year period (2004 to 2013). Current Clinical and Laboratory Standards Institute breakpoints were applied where MIC data were available. Time trends were analyzed using generalized linear mixed models.

Results: We included 8616 unique *E. coli* and *K. pneumoniae* isolates. For *E. coli*, significant ($p < 0.05$) increases in resistance from modeled annual changes were observed for several antibiotics. Cefepime (number of *E. coli* isolates tested for cefepime susceptibility = 3392) resistance increased significantly each year by 16.8%, as did ceftriaxone ($n = 5493$) by 13.1%, ampicillin ($n = 5512$) by 16.0%, cefazolin ($n = 5372$) by 3.7%, and ceftazadime ($n = 4128$) by 7.9%. For *K. pneumoniae*, resistance to imipenem ($n = 2192$) and aztreonam ($n = 1032$) increased significantly by 22.0% and 6.5%, respectively. However, resistance to cefepime ($n = 2059$) decreased significantly each year by 5.5%, ceftriaxone ($n = 3172$) by 7.5%, ciprofloxacin ($n = 2545$) by 6.2%, and gentamicin ($n = 3161$) by 7.7%.

Conclusions: Several concerning increases in resistance were noted for both *E. coli* and *K. pneumoniae*, which can seriously complicate the treatment of these serious infections. Increased antimicrobial stewardship and infection control efforts are warranted to mitigate the emergence of resistance in Enterobacteriaceae.

31. Oral Glucocorticoid and Anti-osteoporosis Medication Use in Commercially Insured Americans (2001–2011)

Robert A. Overman,[1] Margaret L. Gourlay,[2] Chad L. Deal,[4] Joel F. Farley,[1] M. Alan Brookhart,[3] and J. Bradley Layton.[3] *[1]Division of Pharmaceutical Outcomes and Policy—UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA; [2]Family Medicine, University of North Carolina, Chapel Hill, NC, USA; [3]Epidemiology—Gillings School of Public Health, University of North Carolina, Chapel Hill, NC, USA; [4]Rheumatology, Cleveland Clinic Foundation, Cleveland, OH, USA.* *[2]Family Medicine, University of North Carolina, Chapel Hill, NC, USA; [3]Epidemiology—Gillings School of Public Health, University of North Carolina, Chapel Hill, NC, USA; [4]Rheumatology, Cleveland Clinic Foundation, Cleveland, OH, USA.*

Background: Glucocorticoid (GC) use increases osteoporotic fracture risk, and initiation of an anti-osteoporosis medications (AOM) is recommended in chronic (≥90 days) GC use. However, there are limited data on early initiation of AOM among new chronic GC users.

Objectives: The aim of this study was to examine chronic GC use and fill of an AOM within 180 days of chronic GC initiation.

Methods: We identified adult (age ≥ 18) oral GC initiators with initial chronic use in the Truven MarketScan databases (Commercial and Medicare Supplemental) between 2000 and 2012. New users had at least 365 days continuous enrollment prior to first fill of any oral GC and at least 180 days continuous enrollment post-fill. Patients had no prior use of GC or AOM (bisphosphonate, teriparatide, denosumab) or had not been diagnosed with cancer. We estimate rates per 10 000 person years (py) of new GC use and the proportion AOM initiation within 180 days of new GC use in the entire population and then stratified by sex.

Results: There were 32 566 GC initiators who met inclusion criteria. New GC use increased substantially from 0.4 per 10 000 py in 2001 to 3.4 per 10 000 py in 2012, while subsequent use of AOM use decreased substantially from 9.8% in 2001 (high of 13.4% in 2002) to 4.6% by 2012 (figure). Bisphosphonates accounted for 99.9% of the first AOMs used (66.9% alendronate). When stratified by sex, GC utilization was similar for men and women, increasing from 0.4 per 10 000 py in both groups in 2001 to 3.6 in women and 3.2 per 10 000 py in men in 2012. However, concurrent AOM use decreased more sharply in women, beginning at 14.8% in 2001, reaching a high of 17.3% in 2002, and then decreasing to 4.7% in 2012. Male use of AOM was 3.4% in 2001, reached a high of 9.5% in 2007, and then decreased to 4.4% in 2012.

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Conclusions: Prescribed chronic GC therapy increased significantly between 2000 and 2012, while concurrent AOM use decreased. By 2012, the rate of AOM use had fallen to similar levels in men and women, a worrisome trend that could increase preventable osteoporotic fractures attributable to GC use.

32. FDA Drug Safety Announcements' Impact on Use of Bisphosphonates Among Patients with Hip Fracture

Seoyoung C. Kim,[1] Dae Hyun Kim,[1,2] Wesley Eddings,[1] Helen Mogun,[1] Jennifer M. Polinski,[1] Jessica M. Franklin,[1] and Daniel H. Solomon.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA; [2]Gerontology Division, Beth Israel Deaconess Medical Center, Boston, MA, USA.*

Background: Bisphosphonates are the first-line therapy for both prevention and treatment of osteoporosis. The US Food and Drug Administration (FDA) issued several announcements related to potential risk of bisphosphonates including osteonecrosis of the jaw (2005), atrial fibrillation (2007), and atypical femur fracture (2010).

Objectives: The aim of this study was to evaluate the impact of FDA drug safety announcements for bisphosphonates on the use of bisphosphonates in patients with hip fracture in the USA.

Methods: Using claims data from a US commercial health plan (2004–2013), we identified adult patients who had hospitalization for hip fracture. We calculated the proportion of patients who received a bisphosphonate (alendronate, risedronate, ibandronate, and zoledronic acid) or other osteoporosis medication in the 6 months following hip fracture by quarter. Interrupted time-series analyses examined the impact of three FDA announcements on use of bisphosphonates and other osteoporosis medications over time.

Results: There were a total of 28 184 patients who were hospitalized with hip fracture. The mean (SD) age was 64 (21) years, and 61% were female. Overall, the proportion of bisphosphonate use following hip fracture decreased from 15% in 2004 to 6% in 2013. Prior to the FDA announcement in 2007, there was a 3% increase in the odds of bisphosphonate use after hip fracture every quarter (OR 1.03, 95%CI 1.01–1.06). After the announcement in 2007, there was a 4% decrease in the odds of bisphosphonate use (OR 0.96, 95%CI 0.94–0.99) every quarter. The announcement in 2007 was associated with a significant difference in the rate of change of bisphosphonate uses over time ($p < 0.001$), but no impact on other osteoporosis medication use ($p = 0.2$). After the announcement in 2010, the odds of bisphosphonate use continued to decrease by 4% (OR 0.96. 95%CI, 0.94–0.97) each quarter, and the odds of other osteoporosis medication use continued to have a non-significant trend over time (OR 0.98, 95%CI 0.96–1.01).

Conclusions: The FDA safety announcement related to atrial fibrillation was significantly associated with a decrease in trend of bisphosphonate use in patients with hip fracture.

33. Cost and Consequences of Bisphosphonate Non-adherence in an Israeli Population

Inbal Goldshtein,[1,2] Sarah Sharman Moser,[1] Jingbo Yu,[3] Sofia Ish-Shalom,[4] Vanessa Rouash,[1,5] Varda Shalev,[1,2] Ankita Modi,[3] and Gabriel Chodick.[1,2] *[1]Epidemiology and Database Unit, Maccabi Healthcare Services, Tel Aviv, Israel; [2]Tel Aviv University, Tel Aviv, Israel; [3]Global Health Outcomes, Merck & Company, Inc, Whitehouse Station, NJ, USA; [4]Faculty of Medicine, Technion University, Haifa, Israel; [5]Institute of Hypertension, Metabolism, and Endocrinology, Souraski Medical Center, Tel Aviv, Israel.*

Background: The real-world association between sub-optimal adherence with osteoporotic therapy and healthcare costs is important for physicians and policy makers.

Objectives: The aim of this study was to examine the association between bisphosphonate medication adherence and fracture risk, healthcare resource utilization, and costs.

Methods: This was a retrospective analysis of electronic medical records of women aged 55 years or above who started a bisphosphonate between the years 2005 and 2011 in a large health maintenance organization in Israel. Adherence with bisphosphonate treatment was defined as medication possession ratio of 70% or higher during first year following therapy initiation (index). Outcomes of interest included healthcare resource utilization, direct medical cost, and risk of fracture during the second year post-index. Multivariable logistic regression was conducted to

identify the association between adherence and patients' demographic and clinical characteristics. Generalized linear models were used to examine the association between adherence and all-cause healthcare costs.

Results: Among the 17 770 women included in the analysis, aged 66.5 (sd = 8.3) years at index, 80% were treated with alendronate as first line and 20% with risedronate. During the first year of treatment, 48.9% of study patients were not adherent to therapy. Fracture rate during the second year was 2.3% for all patients and differed by age group (3.9% for age 75 years and above vs. 2.1% for younger group, $p < 0.001$) but not by adherence groups (2.1% for adherent patients vs. 2.6% for non-adherent patients, $p = 0.1$). Among patients aged 75 years or over, those that were not adherent to bisphosphonates had an adjusted 41.7% higher risk of fracture compared with adherent patients ($p = 0.018$). Non-adherent patients had 11.9% higher medical costs than their adherent counterparts among patients aged 75 years and above ($p = 0.002$), but not among younger patients.

Conclusions: Non-adherence with bisphosphonates among elderly new users was associated with higher fracture risk and higher medical cost. The results underline the importance of improving the relatively low adherence with osteoporosis treatment, especially among older patients.

34. Chronic Kidney Disease (CKD) Progression Associated with Bisphosphonate (BP) Treatment in Women with Postmenopausal Osteoporosis (PMO)

Fei Xue,[1] Yessenia Bartley,[1] and Chuck Wentworth.[2]
[1]Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA; [2]Analytic Consulting Solutions Inc, Providence, RI, USA.

Background: Food and Drug Administration and Medicines and Healthcare products Regulatory Agency do not recommend bisphosphonate (BP) use in patients with stage 4–5 chronic kidney disease (CKD). It is inconclusive whether BP affects the risk of CKD or worsens existing CKD in patients with no or less severe CKD.

Objectives: The aim of this study was to compare the incidence rate (IR) of CKD progression in patients exposed to BP, other osteoporosis medication (OM), or no OM.

Methods: Women ≥55 years with ≥1 year of enrollment in the UK THIN database (1995–2012) who received an osteoporosis diagnosis or treatment were identified. All patients were followed up for incident CKD progression (i.e., new CKD or increase in CKD stage). Both intent-to-treat analysis comparing initiators of BP or other OM to the untreated and as-treated analysis comparing person-years with on-treatment or on-treatment + post-treatment of BP and/or other OM to the untreated were conducted to assess the effect of BP and other OM. Stratified analysis by baseline CKD stage was conducted in addition to overall analysis.

Results: A total of 22 869 cases of CKD progression were identified in 170 313 women. Relative to the untreated, a higher IR of CKD progression was found in initiators of BP [IRR (95%CI) = 1.20 (1.16–1.24)] but not in initiators of other OM after adjusting for confounders. The higher IR in BP initiators was found in patients without baseline CKD [IRR (95%CI) = 1.19 (1.15–1.23)]. Similarly, a higher IR of CKD progression was associated with on-treatment with BP only [IRR (95%CI) = 1.19 (1.16–1.23)] and BP + other OM [IRR (95%CI) = 1.61 (1.23–2.12)] relative to no treatment after adjusting for confounders. The higher IR associated with on-treatment with BP only and BP + OM was also found in patients with no baseline CKD [IRR (95%CI) = 1.18 (1.15–1.21) and 1.40 (1.04–1.88), respectively] and patients with stages 1–2 [IRR (95% CI) = 1.35 (1.02–1.80) and 4.23 (0.57–31.1), respectively] and stage 3 CKD [IRR (95%CI) = 1.77 (1.41–2.23) and 14.97 (7.14–31.4), respectively]. The results remained similar when extending the time at risk from on-treatment to 1- or 5-year post-treatment period.

Conclusions: BP treatment may increase the risk of new CKD and progression of existing CKD in patients without severe baseline CKD.

35. The Association of Bisphosphonate Use with Incident Tendon Rupture in Patients with or Without Glucocorticoid Comedication

Julia Spoendlin,[1,2] Christian Meier,[3] Susan S. Jick,[4] and Christoph R. Meier.[1,2,4] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Division of Endocrinology, Diabetes and Metabolism, University Hospital Basel, Basel, Switzerland; [4]Boston*

Collaborative Drug Surveillance Program, Boston University, School of Public Health, Lexington, USA.

Background: Bisphosphonates (BP) are the standard care in postmenopausal and glucocorticoid (GC)-induced osteoporosis, but their effects on extraosseous tissue remains sparsely investigated.

Objectives: The aim of this study was to quantify the association of BP use with incident Achilles or biceps tendon ruptures (ATR/BTR) in patients with or without GC comedication.

Methods: We identified patients aged 30 to 90 years with an incident diagnosis of ATR or BTR between 1995 and 2013 in the UK-based Clinical Practice Research Datalink. In a matched (1:4) case–control population, we compared incident exposure with oral BP between cases and controls stratified by GC comedication, substratified by timing (last prescription $</\geq$180 days) and duration (number of prescriptions) of BP use. In a case–crossover analysis, we compared occurrence of BP therapy start between the hazard time period (1 year before ATR/BTR diagnosis) with such occurrence in the control time period (1 year before hazard period) stratified by GC comedication. We applied (multivariate) conditional logistic regression analysis for both analyses.

Results: Among 7859 cases, 334 (4.3%) cases had incident exposure to BP recorded. We observed a significantly increased OR of 5.93 (95%CI 3.70–9.50) for incident short-term BP use ($\leq$4 prescriptions) in patients with GC comedication (irrespective of GC treatment duration). The strength of association linearly decreased with increasing number of BP prescriptions (OR ~ 1.8 for $\geq$20 prescriptions and for past BP use). Incident current oral GC use alone yielded ORs around 2 (in-depth results in separate abstract), whereas BP users without oral GC use yielded ORs around unity across all strata. The case–crossover analysis revealed an OR of 3.12 (95%CI 1.99–4.90) for BP treatment start in patients with GC comedication, whereas BP users without GC use revealed ORs around unity.

Conclusions: We suggest for the first time that BP treatment initiation may transiently augment the risk of tendon rupture in patients with oral GC comedication. Although similar findings in both study designs support the validity of these findings, further studies are needed to confirm a causal association.

36. The Impact of Preadmission Oral Bisphosphonate Use on 30-Day Mortality Following Stroke: A Population-Based Cohort Study

Diana H. Christensen,[1,2] Erzsébet Horváth-Puhó,[1] Morten Schmidt,[1] Christian F. Christiansen,[1] Lars Pedersen,[1] Bente L. Langdahl,[2] Reimar W. Thomsen,[1] and Henrik T. Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark.*

Background: Bisphosphonate use has been associated with increased risk of fatal stroke.

Objectives: The aim of this study was to examine the association between preadmission use of oral bisphosphonates and 30-day mortality following hospitalization for acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).

Methods: We conducted a nationwide population-based cohort study. We identified all patients in Denmark with a first-time hospitalization for stroke between 1 July 2004 and 31 December 2012. Information regarding post-stroke mortality, preadmission oral bisphosphonate use, and potential confounders including age, gender, comedications, and comorbidities was obtained from medical databases. Cox regression was used to compute adjusted hazard ratios as a measure of 30-day mortality rate ratios (MRRs) associated with bisphosphonate current use ($\geq$1 prescription filled within 90 days prior to the stroke), new use (first prescription filled within 90 days prior to the stroke), or recent use (prescription filled in the 90–180 days prior to the stroke). Subgroups of bisphosphonates were examined separately.

Results: We identified 100 043 patients with a first-time hospitalization for stroke. Of these, 83 736 patients had AIS, 11 779 had ICH, and 4528 had SAH. Absolute 30-day mortality risks were increased among current versus non-users of bisphosphonates for AIS (14.6% vs. 10.6%), ICH (43.2% vs. no use 34.5%), and SAH (40.3% vs. 23.2%). In adjusted analyses, bisphosphonate use had no substantial impact on 30-day mortality: AIS (MRR current 0.94, 95% confidence interval (CI): 0.85, 1.04; MRR recent 1.09, 95%CI: 0.89, 1.34), ICH (MRR current 1.09, 95%CI: 0.94, 1.26; MRR recent 1.08, 95%CI: 0.76, 1.54), and SAH (MRR current 1.13, 95%CI: 0.83, 1.55; MRR recent 1.00, 95%CI: 0.47, 2.11). However,

adjusted analyses according to type of bisphosphonate showed increased mortality after stroke among new users of etidronate (MRR 1.45, 95%CI: 1.05; 2.01).

Conclusions: Overall, we found no evidence that preadmission bisphosphonate use increases 30-day mortality following AIS, ICH, or SAH.

37. Covariate Balance Assessment, Model Selection and Bias in Propensity Score Matching: A Simulation Study

M. Sanni Ali,[1,2] Rolf H. H. Groenwold,[1] Svetlana V. Belitser,[2] Kit C. B. Roes,[1] Arno W. Hoes,[1] Anthonius de Boer,[2] and Olaf H. Klungel.[1,2] *[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, The Netherlands.*

Background: In building propensity score (PS) model, inclusion of interaction/square terms in addition to the main terms and the use of balance measures has been suggested. However, the impact of assessing balance of several sets of covariates and their interactions/squares on bias/precision is not well studied.

Objectives: The aim of this study was to investigate the impact of balance assessment with respect to different covariates on bias of the estimated treatment effect and PS model selection.

Methods: Simulation study was conducted using binary treatment and outcome data, and several covariates: confounding terms, risk factors (RFs; only related to outcome), instrumental variables (IVs; only related to treatment), and their interactions/squares. Treatment effects (risk ratios) were estimated using PS matching, and covariate balance was assessed using standardized difference. PS model selection was based on the balance achieved on different sets of covariates, and their interactions/squares. The types of covariates included in balance assessment were compared with respect to bias/precision of the effect estimate as well as the PS model selected.

Results: PS model selection based on balance of confounding variables and RFs provided the least biased estimates. Inclusion of interactions/squares in balance calculation improved the precision of the estimate without increasing the bias. Although PS model selection based on balance calculation on all covariates and on confounding terms as well as IVs resulted in similar estimates in the absence of unmeasured confounding, inclusion of interactions/squares in balance calculation increased the bias (up to 13.6%) while reducing the precision. When PS model was selected based on the balance achieved only on confounding terms, the PS model containing only confounding terms was often selected followed by the PS model with confounding terms and RFs.

Conclusions: In PS model selection based on covariate balance, the choice of covariates and interaction/squares for balance calculation has substantial impact on bias/precision of the treatment effect. Researchers should consider PS model selection based on the balance achieved on confounding variables, RFs and important interactions among confounders and RFs.

38. Comparison of High Dimensional Confounder Summary Scores in Comparative Healthcare Database Studies of Newly Marketed Medications

Hiraku Kumamaru,[1] Joshua J. Gagne,[1] Robert J. Glynn,[1] Soko Setoguchi,[2] and Sebastian Schneeweiss.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Duke Clinical Research Institute, Durham, NC, USA.*

Background: High-dimensional propensity scores (hdPS) facilitate adjustment for many potential confounders but can be limited in comparative studies of new medications shortly after their market entry owing to the small number users and even fewer number experiencing the outcome(s) of interest. High-dimensional disease risk scores (hdDRS) developed in historical cohorts may overcome this problem while still permitting adjustment for many potential confounders.

Objectives: The aim of this study was to compare confounding adjustment by hdPS and historically developed hdDRS in three comparative studies of newly marketed medications: dabigatran versus warfarin on major hemorrhage and on death; and coxibs versus non-selective non-steroidal anti-inflammatory drugs on gastrointestinal bleeds

Methods: In each example, we constructed a concurrent cohort of new and comparator drug initiators using US claims databases. In historical cohorts of comparator

drug initiators, we developed hdDRS models including investigator-specified plus empirically identified variables and using principal component analysis and lasso regression for dimension reduction and shrinkage. We applied the models to the concurrent cohorts to obtain predicted outcome probabilities, which we used for confounding adjustment. We compared the resulting estimates with those from standard hdPS.

Results: The unadjusted odds ratio (OR) comparing dabigatran with warfarin was 0.52 (95% confidence interval: 0.37–0.72) for major hemorrhage and 0.38 (0.26–0.55) for death, and the ORs increased to 0.64 (0.46–0.91) and 0.56 (0.38–0.83), respectively, from conventional regression with predefined variables. Decile stratification by hdDRS yielded an OR of 0.64 (0.46–0.90) for hemorrhage as compared with an OR of 0.70 (0.49–1.02) for hdPS. ORs for death were 0.69 (0.45–1.06) for hdDRS and 0.73 (0.48–1.10) for hdPS. The performance of hdDRS relative to conventional regression and hdPS was similar in the coxib example.

Conclusions: In the examples studied, hdDRS developed in historical cohorts achieved similar or better confounding adjustment compared with conventional outcome regression but worked slightly less well than hdPS.

39. Resampling Methods for Evaluating Disease Risk Scores in Comparative Effectiveness Research

Richard Wyss,[1] Alan R. Ellis,[2] M. Alan Brookhart,[1] and Til Stürmer.[1] *[1]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA; [2]Department of Social Work, North Carolina State University, Raleigh, NC, USA.*

Background: Propensity score (PS) models can be evaluated by assessing covariate balance across treatment groups. Measures of covariate balance cannot be used in the same way to evaluate disease risk score (DRS) models. It remains unclear what metrics are optimal for evaluating DRS models.

Objectives: We compared metrics for evaluating the predictive performance of DRSs and their correspondence with bias in effect estimates. We also examined a recently proposed strategy where DRS models are evaluated by calculating the pseudo-bias within a "dry run" analysis of individuals who are resampled from the control population. We evaluated the discussed concepts using simulations and an empirical example comparing dabigatran versus warfarin in preventing ischemic stroke and all-cause mortality within the Medicare population.

Methods: We simulated 300 scenarios and fit 32 DRS models with various degrees of model misspecification for each scenario. In the empirical example, we fit high-dimensional PS and DRS models. The DRS model was fit within a historical population of new warfarin users. We evaluated each DRS model by calculating the *c*-statistic, the Hosmer–Lemeshow *p*-value, and the pseudo-bias within a "dry run" analysis.

Results: In simulations, the pseudo-bias had the strongest correlation in predicting bias in effect estimates, while the Hosmer–Lemeshow *p*-value had the weakest correlation. In the empirical example, PS and DRS matching resulted in similar hazard ratios of 0.88 (0.81, 0.95) and 0.87 (0.80, 0.94). The fitted PS model had a *c*-statistic of 0.73 and Hosmer–Lemeshow *p*-value of 0.52. The fitted DRS had a *c*-statistic of 0.78 and Hosmer–Lemeshow *p*-value of <0.01. After matching on the PS, treatment groups were balanced on measured covariates with an average standardized absolute mean difference of <0.01. DRS matching resulted in a pseudo-bias of approximately 0.01.

Conclusions: Accurately modeling the DRS presents unique challenges that are not shared by the PS. Measures of predictive performance do not necessarily identify the ability of a DRS model to control confounding. Evaluating the ability of the DRS model to control confounding within a "dry run" analysis can provide insight into the validity of fitted DRS models.

40. Performance of a Disease Risk Score to Predict Clostridium difficile Disease Using Linked Outpatient and Inpatient Dataset: A Study Using CPRD-HES (UK)

Clare Marley,[1] Yassine El Hahi,[2] Adrian Cassidy,[2] and Germano L.C. Ferreira.[2] *[1]GSK, London, UK; [2]GSK Vaccines, Wavre, Belgium.*

Background: A *Clostridium difficile* (CDI) disease risk score was developed in the USA based on inpatient data from two hospitals (NY, CT).

Objectives: The aim of this study was to assess the applicability and predictive value of the existing risk

score to predict risk for CDIFF combining inpatient and outpatient linked data.

Methods: ***Design:*** We performed a cohort study in the UK Clinical Practice Research Datalink–Hospital Episode Statistics (CPRD-HES) linked database. Subjects were 18 years or older enrolled between 2008 and 2012. Index date was defined on the first recorded event (consultation, prescription, diagnosis) after a period of 12 months DB enrolment. Score components were assessed over 90 days prior to index date and 90 days follow-up post-index date for CDI occurrence.

Statistical analysis: Subjects were classified as high or low *CDI* risk using the original score threshold of 4 based on age, hospital admissions, length of stay in hospital and number of antibiotic classes used. The score was applied to 2 492 493 included subjects and tested against the occurrence of *CDI*. *CDI* incidence rates were compared with mandatory surveillance reports by Public Health England (PHE). Receiver-operating characteristics assessed the score-based classification performance. Logistic regression examined the strength of association of *CDI* with each determinant in the risk score.

Results: Trends of *CDI incidence* rate were consistent with PHE estimates for the same time period. The crude odds of *CDI* were 26 times higher in high-risk versus low-risk subjects (crude OR 25.79, 95%CI 13.79–48.24). The sensitivity of the risk score was high (98%), but the specificity was low (35%) with a positive predictive value of 0.03%. Increasing threshold to 7, sensitivity was 80%, and the specificity was 87%. Likelihood ratio test confirmed a significant contribution of each variable in the multivariate regression ($p < 0.0001$).

Conclusions: CPRD-HES linked dataset is a valid dataset to study *CDI*. All variables included in the risk score were associated with risk of *CDI*. The predictive value was low when using the lower original threshold, in part owing to the high weight of age in the scoring algorithm. Increasing the threshold resulted in overall better performance. [ISAC protocol: 14_141]

41. Evaluation of Instrumental Variable Analysis Using Cox Proportional Hazard Model in Pharmacoepidemiologic Studies

Md Jamal Uddin,[1] Rolf H. H. Groenwold,[2] Mohammed Sanni Ali,[2] and Olaf H. Klungel.[3] *[1]Department of Statistics (Epidemiology and Biostatistics), Shahjalal University of Science and Technology, Sylhet, Bangladesh; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Division of Pharmacoepidemiology and Clinical Pharmacology, University of Utrecht, Utrecht, The Netherlands.*

Background: Instrumental variable (IV) analysis using a Cox model has been used to estimate treatment effect in pharmacoepidemiologic studies with survival outcome. However, the performance of the IV analysis is not well known in such cases.

Objectives: The aim of this study was to evaluate the performance of IV analysis using a Cox model in pharmacoepidemiologic settings.

Methods: Simulation studies were performed in several scenarios with varying baseline hazard, rate of censoring, and strength of confounders (hazard ratio (HR) = 1.5 to 5). The IV was time invariant and satisfied its basic assumptions. Moreover, we assumed homogeneous treatment effects to obtain average causal effect of treatment on the outcome. The true treatment effects (HR) of 2 and 1 (null effect) were considered. In each scenario, we considered a sample size of 10 000 with 1000 replications. Treatment effects were estimated using conventional Cox model and two-stage IV models, that is, a Cox model including predicted probability of treatment instead of actual treatment; 95% confidence intervals (CIs) were estimated by the 2.5 and 97.5 percentiles of the 1000 estimates.

Results: The treatment effects based on IV analysis were similar to the true value (HR = 2), HR = 2.02 [95%CI 1.59–2.59], when observed confounders were not adjusted for in the IV models and strength of the confounders were moderate. However, when observed confounders were adjusted for in the IV models, the effect estimates shifted away from the true value, HR = 2.28 [1.77–2.98], owing to non-collapsibility of the HR. In the case of a null treatment effect in all scenarios, the estimates based on the unadjusted and adjusted IV models were similar to the true value (HR = 1). Moreover, estimates from the conventional Cox models were shifted away from the true values in all settings.

Conclusions: Our study suggests that treatment effects from the IV analysis using Cox model can be valid when estimates were reported from the unadjusted IV

models with moderate confounders or the treatment has no effect on the outcome. However, in practical settings, estimates should be interpreted cautiously as IV analysis is sensitive to violations of its assumptions.

42. Instrumental Variable Methods for Continuous Outcomes That Accommodate Non-ignorable Missing Baseline Covariates

Ashkan Ertefaie,[1] Dylan Small,[1] James Flory,[2] and Sean Hennessy.[1] *[1]University of Pennsylvania, Philadelphia, PA, USA; [2]Weill Cornell Medical College, New York, NY, USA.*

Background: Physician prescribing preference has been used as an instrumental variable (PPP IV) to adjust for unmeasured confounding. To provide consistent estimates of treatment effect, variables that affect the IV, treatment, and outcome should be included in the analysis. Ignoring missing values in such variables could bias the effect estimates.

Objectives: The aim of this study was to develop an approach to PPP IVs that can handle non-ignorable missing values in confounders.

Methods: We propose a two-step procedure. In the first step, the IV value is estimated by a complete case analysis using a random effects model that includes IV-treatment confounders. In the second step, the treatment effect is estimated using a two-stage least squares IV approach excluding the IV-treatment confounders with missing values. The proposed method is illustrated in a cohort study of adults treated with oral antidiabetic monotherapy, to compare the effect on body mass index (BMI) of metformin versus sulfonylureas as initial therapy. We included patients who were followed up for at least 180 days without receiving any diabetes drugs, had a recorded HbA1c of 7% or greater, and then were started on an initial therapy. The outcome is the first measurement of BMI after 2 years of follow-up.

Results: We identified 153 694 patients who met inclusion criteria; 77% (117 666) of patients initiated metformin, and 23% (36 028) initiated a sulfonylurea. Baseline BMI was missing for 39% of patients (93 565). An IV analysis that did not include the baseline BMI estimated that, contrary to their known effect, sulfonylureas reduced follow-up BMI by 2.40 (95%CI: 1.94, 2.86), while the proposed method showed a 0.97 point increase (95%CI: 0.09, 1.85) in BMI, which is consistent with their known effect from randomized trials.

Conclusions: The proposed method can be used in settings where there is a significant amount of missing data in IV-treatment confounders. Our analysis shows that the proposed method reduces the confounding bias compared with an IV excluding baseline variables for which some data are missing, and our results confirm the known association of sulfonylureas with weight gain as initial therapy.

43. Estimating the Extent and Predictors of Pharmaceutical Opioid Use in Australia in 2013

Louisa Degenhardt,[1,2] Natasa Gisev,[1] Elena Cama,[1] Briony Larance,[1] and Raimondo Bruno.[3] *[1]National Drug and Alcohol Research Centre, UNSW Australia, Sydney, Australia; [2]School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia; [3]School of Psychology, University of Tasmania, Hobart, Tasmania, Australia.*

Background: There is widespread concern about the global increase in opioid use over the last two decades. To date, available data on the extent of opioid use in Australia have been derived from dispensing claims for prescriptions subsidised by the Australian government. However, these data do not capture non-government subsidised opioids or those that are only available over the counter (OTC), under-estimating the actual extent of use.

Objectives: The aims of this study were to quantify the total use of opioid medicines in Australia and examine geographic and sociodemographic factors that may affect utilisation rates.

Methods: IMS Health national sales data for OTC (codeine) and prescription opioids (oxycodone, morphine, codeine, fentanyl, hydromorphone, methadone, buprenorphine, dextropropoxyphene, tramadol and tapentadol) were used to estimate total utilisation rates in the community during 2013, mapped to Statistical Local Areas (SLAs; a geographical classification defined by the Australian Bureau of Statistics (ABS)). All opioid amounts were measured in unit sales and milligrams then transformed into oral morphine equivalent milligrams (OME mg) for comparison across opioid types. Data on the demographic characteristics of SLAs were obtained from the ABS (sex and age distribution, income, and levels of

physical labour) and other sources (number of pharmacies in SLAs) and were included in linear regression analyses.

Results: An estimated 10 747.24 kg (OME) of pharmaceutical opioids was used across Australia in 2013, equating to 481.16 OME mg per person over the year. There was considerable geographic variation in opioid use; in New South Wales, opioid consumption (OME mg per person) increased by remoteness. Geographic areas that are less populated, have more men and older people, proportionally more low income earning households and greater proportions in jobs requiring physical labour had higher consumption rates.

Conclusions: In 2013, the total opioid use per person in Australia was estimated to be 481.16 OME mg. Considerable geographic variation in opioid utilisation was identified, highlighting a need to understand the reasons and potential issues associated with the use of opioids in Australia.

44. Validation of the Overutilization Monitoring System to Detect Opioid Misuse Using Claims Data

Kathryn Rough,[1,2] Krista F. Huybrechts,[2] Sonia Hernandez-Diaz,[1] Rishi J. Desai,[2] Elisabetta Patorno,[2] and Brian T. Bateman.[2,3] *[1]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [3]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA.*

Background: In response to soaring rates of prescription opioid abuse and overdose in the USA, the Centers for Medicare and Medicaid Services created the Overutilization Monitoring System (OMS) to identify the potential misuse of opioid medications.

Objectives: The aim of this study was to examine opioid utilization patterns and risk of diagnosed opioid abuse and overdose among patients meeting OMS criteria.

Methods: Claims data for incident prescription opioid users were gathered from the Medicaid Analytic eXtract (MAX) for 2000–2010 and United Healthcare for 2003–2013 (excluding children <15 and patients with malignancies). Patients were followed up for 12 months after their first opioid dispensing. Opioid misuse was defined using OMS criteria (daily equivalent of >120 mg morphine for ≥90 consecutive days and use of >3 prescribers and >3 pharmacies for prescription opioids within a year). Opioid abuse and overdose diagnoses were measured using ICD-9 CM codes. Differences in opioid utilization patterns between patients who did and did not meet OMS criteria were summarized, and unadjusted risk ratios (RR) with 95% confidence intervals (CIs) were calculated for diagnosed abuse/overdose.

Results: Of the 6 266 062 eligible individuals in MAX and 4 298 537 in United who received at least one opioid prescription, 0.05% (n = 3,177) and 0.02% (n = 802) respectively met the OMS criteria. Compared with patients not meeting the OMS criteria, those who did were more likely to be dispensed immediate-release oxycodone (MAX: 72.7% vs. 19.9%; United: 88.8% vs. 25.5%), extended-release (ER) oxycodone (MAX: 46.5% vs. 0.6%; United: 50.6% vs. 0.5%), ER fentanyl (MAX: 16.1% vs. 0.4%; United: 15.3% vs. 0.2%), ER morphine (MAX: 30.8% vs. 0.4%; United: 21.0% vs. 0.2%), as well as multiple classes of opioids (MAX: 97.0% vs. 25.6%; United: 94.4% vs. 19.1%). In both cohorts, meeting the OMS criteria was associated with an increased risk of an opioid abuse/overdose diagnosis (MAX: 3.6% vs. 0.2%, RR = 20.1, 95%CI = 16.8–24.1; United: 2.4% vs. 0.1%, RR = 46.2, 95%CI = 29.6–72.2).

Conclusions: In large cohorts of publicly and commercially insured patients, the OMS criteria identified patients who were at a substantially elevated risk of opioid abuse or overdose.

45. Comparison of Abuse and Suicide Rates of Buprenorphine Patch Versus Other Extended-Release Opioid Analgesics in the National Poison Data System Database

Paul M. Coplan,[1,2] Nelson E. Sessler,[1] Hrishikesh Kale,[3] and Venkatesh Harikrishnan.[1] *[1]Risk Management & Epidemiology, Purdue Pharma L. P., Stamford, CT, USA; [2]Epidemiology, Adjunct, University of Pennsylvania, Philadelphia, PA, USA; [3]Health Outcomes, University of Virginia, Charlottesville, VA, USA.*

Background: Both abuse and suicide using prescription opioids are significant public health problems. A 7-day buprenorphine transdermal delivery system/

patch (Butrans®) is indicated for chronic pain treatment is a Schedule III opioid, a drug category with less abuse potential than Schedule II according to the US Controlled Substances Act. Published data on abuse or suicides using a buprenorphine patch are sparse.

Objectives: This study compared the rate of abuse and suicide using Butrans (buprenorphine patch) to other extended-release (ER) opioid analgesics indicated for chronic pain using the National Poison Data System (NPDS), a national network of all US poison centers.

Methods: Calls regarding abuse to all US poison centers, a validated proxy of opioid abuse and overdose, as well as suicides, were collected by NPDS. Rates of calls in the 2 years between July 2012 and June 2014 were calculated for buprenorphine patch and comparator opioids, using prescription adjustment (IMS Health) to account for community availability. Rate ratios and 95% confidence intervals (CIs) were calculated.

Results: The rate of abuse calls to poison centers per million prescriptions was 5 for buprenorphine patch, 50 for fentanyl patch, 34 for ER oxycodone, 108 for ER oxymorphone, and 225 for methadone. The rate of abuse for buprenorphine patch was 10.8-fold lower than for fentanyl patch (rate ratio = 10.8, 95%CI: 4.5–25.9, $p < 0.0001$), 7.2-fold lower than for ER oxycodone (RR = 7.2, 95%CI: 3.0–17.4, $p < 0.0001$), 23.2-fold lower than for ER oxymorphone (95%CI: 9.5–56.2, $p < 0.0001$), and 48.2-fold lower than for methadone (95%CI: 20.1–116.0, $p < 0.0001$). The rate of suicide associated with buprenorphine patch was 2.8-fold lower (95%CI: 1.6–4.9) than with fentanyl patch, 6.2-fold lower (95%CI: 3.5–11.0) than with ER oxycodone, 7.8-fold lower (95%CI: 4.3–14.0) than with ER oxymorphone, and 26.7-fold lower (95%CI: 28.6–31.1) than with methadone.

Conclusions: Calls to US poison centers involving abuse and suicides were significantly lower for buprenorphine patch versus fentanyl patch, ER oxycodone, ER oxymorphone, and methadone, in both absolute number and prescription-adjusted rates.

46. Changes in Diagnosed Addiction Rates in Patients Prescribed OxyContin (ERO) or Other Opioids After Introduction of ERO with Abuse-Deterrent Properties

Paul M. Coplan,[1] and Aditi Kadakia.[1] *[1]Risk Management & Epidemiology, Purdue Pharma L. P., Stamford, CT, USA; [2]Epidemiology, Adjunct, University of Pennsylvania School of Medicine, Philadelphia, PA, USA.*

Background: The impact of opioids with abuse-deterrent properties (ADPs) on addiction rates in patients prescribed opioids has not been assessed. Addiction diagnoses have been shown to have high positive predictive value to detect addiction.

Objectives: The aim of this study was to assess changes in rates of diagnosed addiction among patients prescribed OxyContin® (extended-release or ER oxycodone) after its reformulation with ADPs. Comparator opioids were used to distinguish ER oxycodone-specific changes from general opioid changes.

Methods: Incidence rates of diagnosed addiction per 100 person-years of opioid use were calculated using a commercial insurance database (MarketScan). Addiction was identified by ICD-9 304.0x and 304.7x codes, following DSM-IV classification of addiction as dependence. Changes in rates from 1 year before (August 2009 to July 2010) to 1 year after (November 2010 to October 2011) reformulation were assessed for patients prescribed ER oxycodone or three other opioids. Results were stratified by use of only one opioid or multiple opioids concomitantly because risks differ between these two groups.

Results: From the year before to the year after introduction of reformulated ER oxycodone, rates of diagnosed addiction decreased 27% (95%CI: −37%, −16%, $p < 0.0001$) among patients prescribed ER oxycodone alone, and increased for all three comparators (immediate-release (IR) single-entity (SE) oxycodone +15%, ER oxymorphone +22%, ER morphine +1%). Addiction rates decreased 9% (95%CI: −15%, −3%, $p < 0.0001$) among patients prescribed ER oxycodone with other opioids, while comparators varied (IR SE oxycodone +4%, ER oxymorphone −7%, ER morphine −11%).

Conclusions: Rates of diagnosed addiction among patients prescribed ER oxycodone without other opioids decreased significantly after the introduction of OxyContin® with ADPs, and the decrease differed significantly from that for three comparator opioids. The decrease in diagnosed addiction rates for ER oxycodone was greater when prescribed alone than with another opioid.

47. Trajectories of Buprenorphine Treatment and Associated Emergency Department and Inpatient Use in a Large Medicaid Program

Wei-Hsuan Lo-Ciganic,[1] Walid F. Gellad,[2,3] Adam J. Gordon,[2,3] Gerald Cochrane,[4] and Julie M. Donohue.[5]
[1]Department of Pharmacy, Practice and Science, College of Pharmacy, University of Arizona, Tucson, AZ, USA; [2]Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [3]Center for Health Equity Research and Promotion, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, USA; [4]School of Social Work, University of Pittsburgh, Pittsburgh, PA, USA; [5]Department of Health Policy and Management, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA.

Background: Buprenorphine is an effective treatment for opioid use disorders. However, uncertainty about optimal duration of buprenorphine treatment may lead to substantial variation in provider decision-making, and patient outcomes. In response to the high cost of treatment, some payers have placed limits on treatment duration, although little is known about the impact of these limits. Early discontinuation of buprenorphine due to non-adherence also remains a concern.

Objectives: The aims of this study were to identify distinct trajectories of buprenorphine treatment and examine outcomes associated with these trajectories.

Methods: We analyzed data from a retrospective cohort study of 10 945 adults (18–64 years) Pennsylvania Medicaid enrollees initiating a new episode of buprenorphine treatment between July 2007 and December 2011. We used group-based trajectory models to identify buprenorphine trajectories in the 12 months following buprenorphine initiation. Multivariate Cox proportional hazard models were used to examine the association between trajectories and time to first all-cause hospitalization and first emergency department (ED) visit in the following year.

Results: Six trajectories of buprenorphine treatment were identified: four groups discontinued buprenorphine (24.9% discontinued at <3 months, 18.7% at 3–5 months, 12.4% at 5–8 months, and 13.3% at >8 months); 9.5% refilled intermittently; and 21.2% refilled persistently for 12 months. Factors associated with treatment discontinuation were minority race, having history of frequent ED visits and hospitalizations, and comorbid psychoses. After adjusting for sociodemographics, health status, and provider-level covariates, patients who refilled persistently had a 20% lower risk of all-cause hospitalizations (hazard ratio [HR] = 0.80, 95%CI, 0.68–0.94) and 15% lower risk of an ED visit (HR = 0.85, 95%CI, 0.77–0.94) in the subsequent year, compared with those discontinuing between 3 and 5 months.

Conclusions: Buprenorphine treatment trajectories were highly variable in this large Medicaid cohort. Patients who used buprenorphine persistently for 12 months had lower risk of all-cause hospitalizations and ED visits than those experiencing early discontinuation.

48. The Effect of Treatment and Retention with Opioid Substitution Therapy in Reducing Crime Among Opioid-Dependent People

Natasa Gisev,[1] Sarah Larney,[1,2] Amy Gibson,[3] Jo Kimber,[1] Lucy Burns,[1] Tony Butler,[4] Richard Mattick,[1] Don Weatherburn,[5] and Louisa Degenhardt.[1,6]
[1]National Drug and Alcohol Research Centre, UNSW Australia, Sydney, NSW, Australia; [2]Alpert Medical School, Brown University, Providence, RI, USA; [3]Centre for Big Data Research in Health, UNSW Australia, Sydney, NSW, Australia; [4]The Kirby Institute, UNSW Australia, Sydney, NSW, Australia; [5]Bureau of Crime Statistics and Research, Sydney, NSW, Australia; [6]School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia.

Background: People with opioid dependence are known to have increased contact with the criminal justice system. Although there is strong evidence for the health and social benefits of opioid substitution therapy (OST), the relationship between OST treatment and crime is less clear.

Objectives: The aims of this study were to evaluate the effect of OST on time to first offence and overall crime rates among opioid-dependent people and examine the relationship between retention in OST and crime rates.

Methods: We used retrospective data linkage study of 10 744 entrants into OST in New South Wales (2004–2010) to offences, custody episodes and death notifications, up to 31 December 2011. Time-dependent Cox proportional hazards models were used to examine the association between OST exposure and the time to first offence, adjusting for demographic covariates. Crude crime rates (CCRs) in the 4 years prior to treatment entry, and periods in and out of OST were also computed, and the effect of treatment retention was evaluated at 3, 6, 9 and 12 months.

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Results: In total, 5751 (53.5%) treatment entrants were charged with an offence during the observation period. The unadjusted hazards ratio for the risk of offending for the first time after starting treatment was 0.82 (95%CI 0.78–0.87), and after adjusting for demographic covariates, the hazards ratio was 0.87 (95%CI 0.83–0.92). The CCR per 100 person-years prior to treatment entry was 130.78 (95%CI 129.65–131.91). The CCR decreased by 32% while individuals were in OST (CCR 88.29, 95%CI 86.96–89.63) and 20% out of OST (CCR 101.67, 95%CI 100.35–102.99). The CCR was further reduced the longer the treatment: 85.72 (95%CI 84.40–87.05) at 3 months, 82.78 (95%CI 81.48–84.10) at 6 months, 79.20 (95% CI 77.91–80.50) at 9 months and 76.50 (95%CI 75.22–77.80) at 12 months.

Conclusions: OST treatment was associated with a reduction in the risk of offending for the first time after commencing treatment. Entry into OST was also associated with lower overall crime rates, with the greatest reductions observed among people who were retained longer in treatment.

49. Effects of Gene Expression Profiling on Adjuvant Chemotherapy Use in Women Under Age 65 With Breast Cancer

Arnold L. Potosky,[1] Suzanne C. O'Neill,[1] Claudine Isaacs,[1] Calvin Chao,[2] Huei-Ting Tsai,[1] Chunfu Liu,[3] Bola F. Ekezue,[3] Nandini Selvam,[3] Larry G. Kessler,[4] and Marc D. Schwartz.[1] *[1]Oncology, Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC, USA; [2]Genomic Health Inc., Redwood City, CA, USA; [3]HealthCore, Inc., Alexandria, VA, USA; [4]University of Washington School of Public Health, Seattle, WA, USA*

Background: Gene expression profiling (GEP) was introduced into US practice in 2005 as a promising method to help predict the risk of breast cancer recurrence and guide decisions about adjuvant chemotherapy. There are little data on the dissemination of this test and its association with adjuvant chemotherapy use in community oncology practice.

Objectives: We evaluated the prevalence of testing and the relationship of GEP testing with use of adjuvant chemotherapy.

Methods: We conducted a retrospective observational cohort study of women ages 24–64 newly diagnosed with early-stage hormone-receptor positive breast cancer between 2006 and 2012 ($n = 9405$) in a large commercial insurance plan. We created a new linked dataset consisting of cancer registry data from five states, health claims data, and GEP test results. We use logistic regression to assess the association of test results with adjuvant chemotherapy use among the 2362 tested women in our cohort.

Results: Rates of testing for women with node negative disease increased from 20.4% in 2006 to 35.2% in 2011. The proportions of tested women with low, intermediate, and high Oncotype DX® Recurrence Score@ GEP test results were 51%, 39%, and 10%, respectively. Among these women, 11%, 47%, and 88% received adjuvant chemotherapy, respectively. Recurrence Score values were significantly and positively associated with chemotherapy use over the full range of the score, and there was a significant, positive linear relationship of scores with chemotherapy use within the low and intermediate sub-groups after adjusting for age and other clinical factors.

Conclusions: In an insured population of women under age 65, GEP testing rapidly increased following its inclusion in guidelines. The use of adjuvant chemotherapy following GEP testing is concordant with recommended test interpretation for 89% of women at either high or low risk of recurrence. Chemotherapy use in the intermediate risk group increased with Recurrence Score values. Evidence from ongoing randomized trials may help clarify whether this finding reflects optimal use of GEP testing in intermediate risk women.

50. Patient Population with Multiple Myeloma and Transitions Across Different Lines of Therapy in the US: An Epidemiologic Model

Javier Cid Ruzafa,[1] Evie Merinopoulou,[1] Rebecca F. Baggaley,[2] Pamela Leighton,[1] Winifred Werther,[3] Diana Felici,[3] and Andrew Cox.[1] *[1]Evidera, London, UK; [2]London School of Hygiene & Tropical Medicine, London, UK; [3]Onyx Pharmaceuticals, San Francisco, CA, USA.*

Background: Multiple myeloma (MM) is an incurable disease with current treatments intended to delay symptomatic disease progression.

Objectives: Our objective was to forecast the number of patients with MM per line of therapy in the USA

and the number of new patients initiating each line of therapy over 12 months.

Methods: We used a compartmental model representing the flow of patients with MM from disease occurrence to death. The model utilized a set of four differential equations to distinguish two possible treatment pathways (eligible for stem cell transplantation or not), four patient subgroups (≥65 years or younger, at high cytogenetic risk or at low/standard risk), and up to 17 states in each subgroup (states representing each line of therapy). Incidence of MM from the Surveillance Epidemiology and End Results Cancer Statistics and mortality rates from the US National Vital Statistics were used. Patients with asymptomatic MM and those with symptomatic MM before treatment initiation were also considered. We derived treatment line transition rates from published data on progression-free survival, time to tumor progression, and overall survival. The base-case scenario was defined, and the model was run to equilibrium (at which point the numbers of patients on each line remain stable). Model output included 95% credible intervals (CIs) from probabilistic sensitivity analyses.

Results: The current forecasted total number of patients with MM in the USA over a 12-month period was 80 219, of whom 70 375 were predicted to be on active treatment, 23 629 (CI: 22 236–25 029) on first-line therapy, and 15 350 (CI: 13 845–16 760) on second-line therapy. Over 1 year, 18 689 and 14 423 patients diagnosed with MM were forecasted to initiate first-line and second-line therapies, respectively, and the forecasted total mortality among patients with MM was 19 330.

Conclusions: The size of the US patient population with MM on different lines of therapy and across patient subgroups of interest was estimated from an epidemiologic model. These estimates can be used to assess the number of patients who could benefit from new therapies and their budgetary impact.

51. Risk of Esophageal or Gastric Cardia Cancer in Elderly Medicare Beneficiaries Treated with Oral Bisphosphonates

David J. Graham,[1] Andrew E. Howery,[2] Jacqueline M. Major,[1] Diqiong Xie,[1] Vedita Bipat,[2] David Moeny,[1] Stephen Voss,[1] Jessica Young,[2] Ling Lan,[1] Thomas E. MaCurdy,[2,3] Chris Worrall,[4] and Jeffrey A. Kelman.[4]

[1]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [2]Acumen, LLC, Burlingame, CA, USA; [3]Stanford University, Stanford, CA, USA; [4]Centers for Medicare & Medicaid Services, Washington, DC, USA.

Background: Observational studies have yielded conflicting results for risk of esophageal cancer with oral bisphosphonates (OBP).

Objectives: The aim of this study was to test for an association between OBP use and esophageal or cardia cancer (ECC), accounting for dose and latency.

Methods: A nested case–control study was performed using US Medicare data from 2007 to 2013. Cases of ECC were identified using a validated algorithm based on linkage of Surveillance, Epidemiology and End Results (SEER) registry cases to all Medicare recipients residing in SEER zip codes (sensitivity 89%, positive predictive value 87%). Each case was matched with up to three controls on age, sex, length of Medicare enrollment, low income status, and hospital referral region. Conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for the association of OBP use and ECC. We performed 1- and 2-year lagged analyses adjusted for multiple potential confounders in addition to matching factors. Duration and dosing frequency of OBP use were examined. All analyses were performed separately in men and women, using no OBP use as reference.

Results: Alendronate accounted for ≥95% of OBP use in women and men. In the 1-year lagged analysis, there were 12 236 ECC cases, with no significant association between OBP use and ECC in women. In men, ECC risk was increased with cumulative OBP use ≥2 years (OR 1.71, 95%CI 1.05–2.78). In the 2-year lagged analysis, there were 8776 ECC cases, with no significant association between OBP use and ECC in women. In men, the OR (95%CI) for ECC was 1.38 (1.07–1.79) with any OBP use; 1.12 (0.79–1.61) with <6 months of OBP; 1.34 (0.79–2.29) with 6–12 months of OBP; 1.97 (1.12–3.47) with 1–2 years of OBP; and 2.00 (1.07–3.74) with ≥2 years OBP use. Nearly all OBP use was as weekly dosing, with OR = 1.43 (95% CI 1.09–1.88). There was no evidence of effect modification by Barrett's esophagus in women or men.

Conclusions: OBP use of 1 year or longer duration was associated with an increased risk of ECC in men after a latency of 2 years. Risk was not increased in

women. Further research is needed to explore the basis for this gender difference.

52. Cancer Rates over Time After Initiation of Overactive Bladder Drugs

James A. Kaye,[1] Andrea V. Margulis,[2] Estel Plana,[3] Brian Calingaert,[4] Susana Perez-Gutthann,[2] and Alejandro Arana.[2] *[1]Epidemiology, RTI Health Solutions, Waltham, MA, USA; [2]Epidemiology, RTI Health Solutions, Barcelona, Spain; [3]Biostatistics, RTI Health Solutions, Barcelona, Spain; [4]Epidemiology, RTI Health Solutions, Research Triangle Park, NC, USA.*

Background: Genitourinary cancers may cause symptoms similar to those of overactive bladder (OAB). We investigated incidence rates (IRs) of genitourinary cancers and of other common cancer types among initiators of antimuscarinic OAB drugs, taking into account time since first prescription.

Objectives: The aim of this study was to estimate IR of the 10 most common cancers stratified by time after initiation of treatment.

Methods: Using the Clinical Practice Research Datalink, we assembled a cohort of new users of oxybutynin, tolterodine, solifenacin, fesoterodine, trospium, or darifenacin in 2004–2012 aged ≥18 years and not known to have cancer before cohort entry. Follow-up (FU) ended with cancer diagnosis, death, disenrollment, or end of study period. Cancer diagnoses were identified in primary care, cancer registry, and/or hospitalization records. Crude IR per 1000 person-years and 95% confidence interval (CI) were estimated by year since cohort entry (YSCE) for each study cancer (bladder, breast, colorectal, lung, melanoma, non-Hodgkin lymphoma (NHL), pancreas, prostate, renal, and uterine).

Results: Of 119 913 new users of study drugs (mean age at cohort entry 62 years; 70% women), 4117 with incident study cancers were identified during 399 375 person-years of FU (534 bladder, 886 breast, 545 colorectal, 495 lung, 182 melanoma, 144 NHL, 138 pancreas, 932 prostate, 125 renal, and 136 uterine). Bladder cancer IR (95%CI) was greater in earlier periods: 2.5 (2.2–2.8) <1 YSCE, 1.2 (0.9–1.4) 1 to <2 YSCE, and ≤1 in most later years. Prostate cancer IR was 14.2 (12.9–15.6) <1 YSCE, and 6.8 (5.8–7.9) 1 to <2 YSCE, and then decreased more gradually. IRs were higher <6 months after OAB drug start: bladder 3.5 (3.0–4.0) and prostate 19.5 (17.5–21.8). In contrast, risk of other cancers did not show this effect of time since cohort entry.

Conclusions: Patterns of change in IR over time since cohort entry must be considered in etiologic studies of cancer risk related to use of OAB drugs. Protopathic bias and detection bias are plausible explanations for higher IRs of bladder and prostate cancers during the first few years after starting OAB drug treatment than in subsequent periods.

53. Preliminary Results of Bladder Cancer Risk in Relation to Exposure to Pioglitazone Among Patients with T2DM in the Pan European Multi-database Bladder Cancer Risk Characterisation Study

Pasi Korhonen,[1] Edith M. Heintjes,[2] Rachael Williams,[3] Fabian Hoti,[1] Solomon Christopher,[1] Maila Majak,[1] Irene Bezemer,[2] Leanne Houweling,[2] Helen Strongman,[3] Timothy Williams,[3] Marie Linder,[4] Paul Dolin,[5] and Shahram Bahmanyar.[4] *[1]EPID Research, Espoo, Finland; [2]Pharmo Institute for Drug Outcomes Research, Utrecht, The Netherlands; [3]The Clinical Practice Research Datalink Group, The Medicines and Healthcare Products Regulatory Agency, London, UK; [4]Centre for Pharmacoepidemiology, Karolinska Institute, Stockholm, Sweden; [5]Takeda Development Centre Europe, London, UK.*

Background: This observational cohort study was conducted at the request of the European Medicines Agency in Finland, the Netherlands, Sweden and UK.

Objectives: The objective was to evaluate the bladder cancer risk in T2DM patients in relation to exposure to pioglitazone.

Methods: A common study protocol and pooled analysis plan was used across countries. Linked prescription, hospital, general practitioner, cancer and death registration records were used to build the study database from the country specific datasets. To limit channelling bias, pioglitazone exposed ($n = 56\,337$) and non-exposed were matched based on treatment history and propensity scores, accounting for variables affecting pioglitazone initiation. The hazard ratios (HR) with 95% confidence intervals (CIs) were estimated using Cox's model with adjustments for relevant confounders. Follow-up was from cohort entry until first incident bladder cancer, death, start

of other thiazolidinediones, diagnosis of secondary malignant neoplasm of bladder, leaving from database, end of database coverage or 30 June 2011, whichever occurred first.

Results: A total of 283 bladder cancer cases occurred: 130 in the exposed group during a mean follow-up time of 2.9 years and 153 in the non-exposed group during a mean follow-up time of 2.8 years. The pooled adjusted HR (exposed vs. non-exposed) was 0.99 (95%CI: 0.75, 1.30). The dataset-specific HRs varied from 0.60 (95%CI: 0.33, 1.08) for the Finnish dataset to 4.10 (95%CI: 1.21, 13.87) for the Swedish dataset. Increasing duration and dose were not associated with increasing risk of bladder cancer. The adjusted HRs varied from 1.11 (95%CI: 0.82, 1.49) to 0.81 (95% CI: 0.42, 1.56) for <18 and >48 months of exposure, and from 1.05 (95%CI: 0.77, 1.42) to 0.61 (95%CI: 0.32, 1.20) for 1–14 000 and >48 000 mg of exposure, respectively, when compared with the never-exposed group.

Conclusions: This large pan European study found that pioglitazone use was not associated with increased risk of bladder cancer. Further analyses are needed to explore the observed heterogeneity between datasets.

54. Chronic Use of Lithium Is Safe with Regard to the Development of Kidney and Urinary Tract Cancers

Anton Pottegård,[1] Jesper Hallas,[1] Boye L. Jensen,[2] Kirsten Madsen,[2,3] and Søren Friid.[4,5,6] *[1]Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark; [2]Department of Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; [3]Department of Pathology, Odense University Hospital, Odense, Denmark; [4]Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark; [5]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [6]Institute of Clinical Medicine, Faculty of Health, Aarhus University Hospital, Aarhus, Denmark.*

Background: Lithium induces proliferation in the epithelium of renal collecting ducts. A recent small-scale cohort study reported a strong association between use of lithium and increased risk of renal neoplasia.

Objectives: The aim of this study was to study the association between long-term use of lithium and risk of upper urinary tract cancer (UUTC), including renal cell cancer and cancers of renal pelvis or ureter.

Methods: Using the powerful Danish nationwide registries and a case–control approach, we identified all histologically verified UUTC cases in Denmark between 2000 and 2012 from the Danish Cancer Registry. A total of 6477 cases were matched on age and gender to 259 080 cancer-free controls. Data on lithium use were obtained from 1995 to 2012 from the Danish Prescription Registry. We estimated the association between long-term use of lithium (≥5 years) and risk of UUTC using conditional logistic regression with adjustment for potential confounders.

Results: Long-term use of lithium was observed among 0.22% of cases and 0.17% of controls. This yielded an overall adjusted odds ratio (OR) of 1.3 (95%CI: 0.8–2.2) for UUTC associated with long-term use of lithium. Analyses stratified by stage and subtype of cancer displayed a slightly increased risk of localized UUTC (OR 1.6, 95%CI: 0.8–3.0) and renal pelvis/ureter cancers (OR 1.7, 95%CI: 0.5–5.5).

Conclusions: In our nationwide case–control study, use of lithium was not associated with an increased risk of UUTC.

55. Beta Blockers and the Risk of Suicide in the Elderly

Jonathan S. Zipursky,[1] Erin Macdonald,[2] Simon Hollands,[2] Tara Gomes,[2,3] Muhammad Mamdani,[2,3] J. Michael Paterson,[2,4] and David N. Juurlink.[2,5] *[1]Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Institute of Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [4]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada; [5]Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Background: Beta-adrenergic antagonists (β-blockers) are commonly used among the elderly, but concerns have been raised about their potential association with suicide risk. Lipophilic β-blockers enter the central nervous system readily and may increase the risk of depression and suicidality relative to hydrophilic β-blockers.

Objectives: The aim of this study was to determine whether the use of lipophilic β-blockers is associated with an increased risk of suicide in the elderly.

Methods: We conducted a population-based case–control study of multiple healthcare databases in Ontario, Canada, from 1 January 1993 to 31 December 2011. Cases were Ontarians aged 66 years or older who died of suicide within 100 days of receipt of a prescription for a β-blocker. For each case, we identified up to four controls who also received a β-blocker prescription in the preceding 100 days, matching on age, sex, documented hypertension and a hospitalization for coronary artery disease in the preceding year. We identified all outpatient prescriptions for oral β-blockers, categorizing each as high, intermediate or low lipophilicity based on the partition coefficient for each. We used conditional logistic regression to estimate the odds ratio for the association between suicide and type of β-blocker prescribed, with hydrophilic β-blockers as the reference group. To test the specificity of our findings, we examined the association between β-blocker lipophilicity and death from lymphoma.

Results: We identified 385 individuals who died of suicide within 100 days of receiving a prescription for a β-blocker and 1540 matched controls. Use of lipophilic β-blockers (propranolol or labetalol) was associated with a more than two-fold increase in the risk of suicide (adjusted odds ratio 2.42; 95% confidence interval 1.40 to 4.19) relative to hydrophilic β-blockers. No increased risk was observed with β-blockers of intermediate lipophilicity. As expected, we found no association between β-blocker lipophilicity and death from lymphoma.

Conclusions: The lipophilic β-blockers propranolol and labetalol are associated with an increased risk of suicide in the elderly. Clinicians should be aware of this association, particularly in elderly individuals with other risk factors for suicide.

56. Care Gaps in Glucocorticoid-Induced Osteoporosis Management Among Seniors in Ontario, Canada

Jordan M. Albaum,[1] Linda E. Levesque,[2] Andrea S. Gershon,[3] Guoyuan Liu,[2] and Suzanne M. Cadarette.[1]
[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Queen's University, Kingston, ON, Canada; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

Background: Glucocorticoid (GC) therapy is the most common cause of secondary osteoporosis. As a result, clinical practice guidelines recommend that all patients starting oral GC therapy for ≥3 months receive bone mineral density (BMD) testing and/or osteoporosis treatment.

Objectives: The aim of this study was to examine the proportion of chronic oral GC users that receive osteoporosis management (BMD test and/or osteoporosis treatment) by sex, indication for therapy, and over time.

Methods: We identified all community-dwelling chronic oral GC users aged 66 years or older in Ontario using healthcare utilization data from January 1996 to September 2012. Chronic oral GC use was defined as ≥2 oral GC prescriptions dispensed and ≥450 mg prednisone equivalent over a 6-month period. Osteoporosis management by BMD test and/or osteoporosis treatment within 6 months of starting chronic GC therapy was examined by sex, year, indication for therapy, and osteoporosis management history. Results were summarized using descriptive statistics.

Results: We identified 72 099 male and 95 975 female patients on chronic oral GC therapy (mean age = 74.9 years, SD = 6.5). Approximately two-thirds of chronic GC users ($n = 109\,888$) received ≥900 mg within the 6-month chronic use window. The most common indications for chronic GC therapy were respiratory (43%) and rheumatic (15%) disease. GC-induced osteoporosis management increased from 2% to 23% (men) and from 10% to 48% (women) between 1996 and 2007 but remained stable through to 2012. A higher proportion of patients with prior osteoporosis management was managed within 6 months (56% men and 67% women) compared with patients without prior osteoporosis management (12% men and 23% women). Patients with rheumatic disease were managed most commonly (41%), while respiratory patients were managed least commonly (21%).

Conclusions: GC-induced osteoporosis management improved significantly over time in both sexes yet remains low. Significant care gaps by sex and between clinical areas represent a missed opportunity for fracture prevention among patients requiring chronic GC therapy. Targeted interventions are needed to reduce the burden of fracture-related morbidity associated with chronic GC use.

57. The Impact of a Communication-Training Program on Reductions in Nursing Home Antipsychotic Use

Jennifer Tjia,[1] Laurie Herndon,[2] Carolyn Blanks,[2] Kate Lapane,[1] and Susan Wehry.[3] *[1]Quantitative Health Sciences, University of Massachusetts, Worcester, MA, USA; [2]Massachusetts Senior Care Foundation, Newton Lower Falls, MA, USA; [3]Department of Disabilities, Aging, and Independent Living, State of Vermont, Waterbury, VT, USA.*

Background: Off-label antipsychotic prescribing in nursing homes (NHs) is common, despite modest evidence of efficacy and known risks included on US Food and Drug Administration black box warnings. Efforts to reduce antipsychotic use in NHs have had limited success.

Objectives: The aim of this study was to quantify the effect of a communication-training program on NH antipsychotic use.

Methods: We conducted a quasi-experimental, longitudinal study between September 2012 and September 2013 in 106 Massachusetts NHs, of which 27 were the highest antipsychotic prescribing NHs. Participating NHs used the OASIS educational program that targets all NH staff (direct and indirect) using a train-the-trainer model. The goals of the program are to reframe challenging behaviors of residents with cognitive impairment as communication of unmet needs, to train staff to anticipate resident needs, and to integrate residents' strengths into daily care plans. We used an interrupted time-series model of facility-level prevalence of antipsychotic medications with external controls from both Massachusetts and New York facilities to evaluate the intervention's effectiveness. The 18-month pre-intervention (baseline) period was compared with three post-intervention periods: an initial 3-month training period, a 6-month implementation period, and a 3-month maintenance period.

Results: In the OASIS facilities, baseline prevalence dropped from 31.4% to 26.0% at the end of the study (absolute reduction: 5.4%; relative reduction: 17%). In the control facilities, baseline prevalence dropped from 22.5% to 19.2% (absolute reduction of 3.3%; relative reduction: 14.7%). The OASIS facilities had a greater decline than control facilities in the 6-month implementation period (−0.82%/month [95%CI −1.65% to 0.03%], $p = 0.06$). In a sensitivity analysis removing the top 27 prescribing facilities, the OASIS facilities had a greater decline than control facilities that was statistically significant (−0.97%/month [95%CI −1.89% to −0.06%], $p = 0.04$).

Conclusions: The OASIS communication intervention significantly reduces antipsychotic use compared with controls; its most measurable impact is in the 6-month implementation period following the initial 3-month training period.

58. The Effect of Warning Symbols in Combination with Education on the Frequency of Erroneously Crushing Medication in Nursing Homes

Katja Taxis,[1] Steven Van Welie,[1,2] Tim Beerden,[2] Jasperien Van Doormal,[2] and Linda Wijma-Vos.[2] *[1]Pharmacy, Unit of Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands; [2]Clinical Pharmacy, Martini Hospital, Groningen, The Netherlands.*

Background: Residents of nursing homes often have swallowing difficulties (dysphagia), which makes it difficult to administer solid oral dosage formulations. Crushing medication is a common medication error.

Objectives: We evaluated the effect of warning symbols in combination with education on the frequency of erroneously crushing medication.

Methods: This was a prospective intervention study with a pre- and post-intervention measurement. The study was conducted on 18 wards (total of 200 beds) in three nursing homes in the North of the Netherlands. The intervention consisted of a set of warning symbols printed on each patient's unit dose packaging indicating whether or not a medication could be crushed as well as education of ward staff (lectures, newsletter and poster). Data were collected using direct (disguised) observation of nurses during drug administration. A crushing error was defined as a medication that was crushed, which should not be crushed based on standard reference sources. The main outcome was the relative risk (RR) of crushing errors in the post-intervention compared with the pre-intervention period.

Results: We observed 36 nurses/nursing assistants (92% female; 92% nursing assistants) administering medication to 197 patients (62.9% female; mean age 81.6). The crushing error rate decreased from 3.1% (21 wrongly crushed medicines out of 681 administrations) to 0.5% (3/636), RR = 0.15 (95%CI 0.05–0.51). Medications that were erroneously crushed included enteric-coated formulations (e.g. omeprazole), medication with regulated release systems (e.g. Persantin®; dipyridamol) and toxic substances (e.g. finasteride).

Conclusions: Warning symbols combined with education were a powerful means to reduce erroneous crushing of medication, a well-known and common problem in nursing homes. We recommend wider implementation of this intervention to improve patient safety.

59. Using Data to Change Drug Utilization in the Real World

Lisa G. Pont,[1] Christine Veal,[2] Andrew Flemming,[3] Lee-Fay Low,[4] and Sonali Pinto.[3] *[1]Australian Institute of Health Innovation, Macquarie University, Sydney, NSW, Australia; [2]Webstercare, Sydney, NSW, Australia; [3]Southern Cross Care, Sydney, NSW, Australia; [4]University of Sydney, Sydney, NSW, Australia.*

Background: Using data to drive practice change is commonly used in the research world, yet using data to support change in the real-world presents unique challenges.

Objectives: The aim of this study was to design, develop and evaluate a data-driven evidence-based intervention for changing anti-psychotic use for behavioural and psychological symptoms of dementia (BPSD) in residential aged care.

Methods: A mixed methods approach was utilized. Qualitative data regarding attitudes to antipsychotics were collected via focus groups, and thematic analysis was used to identify local potential barriers and facilitators for change at each site. A suite of evidence-based multidisciplinary interventions was implemented across 26 residential aged care facilities (1800 residents) commencing February 2014. Strategies were developed at the organizational, facility and individual health professional levels and included audit and feedback, education, support, skills training and policy changes. Administrative medication supply data were used to provide audit and feedback at the facility level as well as to evaluate the program. Changes in the number of antipsychotic users were analyzed using Cochran's Q and changes in the number of defined daily doses (DDDs) analyzed using a linear mixed model.

Results: The median facility size was 45 beds, and 21 pharmacies supplied medications to the 26 facilities. The qualitative analysis identified a number of challenges regarding the use of antipsychotics in aged care including lack of awareness regarding the risks of antipsychotics and poor confidence in managing resident behaviour without using antipsychotics.

The total number of antipsychotic users decreased from 9.5% to 4.5% over the 6-month intervention period ($p = 0.000$). For dosing, the total number of DDDs decreased from 0.342 to 0.194 ($p = 0.000$) over the same period.

Conclusions: Antipsychotic use for BPSD decreased significantly following implementation of a data-driven evidence-based approach. Using data to understand the barriers to change and individualize interventions to support local needs based on local site needs allows complex interventions to be conducted to improve quality use of medicines and drug utilization in the real world.

60. Changes in Drug Utilization at the End of Life

Lisa G. Pont,[1] Heleen van der Meer,[2] Gerard Stevens,[3] Andrew McLachlan,[4] and Katja Taxis.[2] *[1]Australian Institute of Health Innovation, Macquarie University, Sydney, NSW, Australia; [2]Faculty of Pharmacy, University of Groningen, Groningen, The Netherlands; [3]Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia; [4]Webstercare, Sydney, NSW, Australia.*

Background: Medications have a pivotal role in the prevention and management of many conditions. The decision to use a medicine in older populations involves consideration of a number of elements in addition to the traditional risk/benefit elements. While it can be expected that the goal of medications at the end of life may changes from disease prevention to symptomatic control, little is known about the patterns of medication use at the end of life and if changes in medication reflect potential changes in clinical need.

Objectives: The aim of this work was to explore changes in the utilization of preventive and symptomatic medications at the end of life in a cohort of elderly nursing home residents.

Methods: A retrospective observational cohort study of nursing home residents ($n = 3876$) from 26 residential aged care facilities in the Sydney metropolitan area was conducted using pharmacy medication supply data. Patients aged ≥65 years who died in the nursing home between June 2008 and June 2010 were included in the analysis. Medications were classified as symptomatic, preventive or other. A linear mixed model was used to compare the use of symptomatic and preventive medication in their last year of life.

Results: Of the 3876 nursing home residents present in the cohort, 554 (14.3%) died within the study period and were included in the analysis. There were distinct differences in utilization of symptomatic and preventive medicines in the last year of life. Symptomatic medication use increased from 4.65 medications per resident 1 year before death to 5.18 medications at death (95%CI 4.43–4.88 vs. 4.96–5.41, $p = 0.000$), while preventive medication use decreased from 1.96 to 1.40 medications (95%CI 1.83–2.10 vs. 1.26–1.53, $p = 0.000$). The duration of use of symptomatic medications was longer than that for preventive medicines (283.0 days (95%CI 273.7–292.3) vs. 257.3 days (95%CI 246.8–267.8), $p = 0.000$).

Conclusions: The results suggest that some consideration is given to changing clinical need at the end of life, yet changes were small. Current healthcare structures in aged care may limit the ability to be responsive to changed clinical need at the end of life.

61. Cost Effectiveness of Amitriptyline Versus Duloxetine in the Treatment of Painful Diabetic Neuropathy in India

Dipika Bansal,[1] and Anil Bhansali.[2] *[1]National Institute of Pharmaceutical Education and Research, SAS Nagar, India; [2]Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

Background: Amitriptyline and duloxetine are the first choice of drugs for the management of painful diabetic neuropathy (PDN). However, the overall cost effectiveness of these drugs is not assessed.

Objectives: We performed the cost-effectiveness of amitriptyline versus duloxetine for treatment of PDN.

Methods: A decision analytic model developed in TREEAGE Pro 2014 was used to analyse the cost-effectiveness of amitriptyline and duloxetine in PDN. The data related to cost and effectiveness were taken from a randomised, double-blind, cross-over clinical trial published by Kaur et al. The work was carried out by the same research team in India. The two drugs, amitriptyline 25 mg/day and duloxetine 60 mg/day, were compared. Duration of treatment was 6 weeks. Proportion of patients attaining to effective pain relief (EPR) for 6 weeks' period was considered as the efficacy end point. Only direct cost was considered for the present analysis. EPR is defined as >50% pain reduction from baseline on VAS 0–10 scale. The utility data were taken from published studies. One-way sensitivity analyses were performed to explore the impact of uncertainty factors in this cost-effectiveness analysis. A tornado diagram was also drawn.

Results: Probability of treatment success (EPR) in amitriptyline and duloxetine arm is 0.55 and 0.59, respectively. Probability of adverse events (AE) for amitriptyline and duloxetine arm is 0.5 and 0.24, respectively. A utility for treatment success (EPR) includes 0.7. The cost per quality adjusted life year (QALY) gained is 10.79 international normalized ratio (INR) for amitriptyline treatment, which is 48.85 INR less than for duloxetine treatment (59.64 INR). The incremental effectiveness is 0.10 QALY, and incremental cost-effectiveness ratio is 491.05 INR/QALY. The results were stable even after sensitivity analysis.

Conclusions: Both amitriptyline and duloxetine are found to have similar efficacy. Duloxetine-treated patients were less prone to AE than patients treated with amitriptyline. In terms of cost comparison, amitriptyline dominates duloxetine. Therefore, amitriptyline provides a cost-effective alternative in painful diabetic neuropathy.

62. Individualized NSAID Prescribing Based on Gastrointestinal and Cardiovascular Risks: A Decision Model in the SOS Project

Gwen M.C. Masclee,[1,2] Vera E. Valkhoff,[1,2] Huub Straatman,[3] Ron Herings,[3] Edeltraut Garbe,[4] Tania Schink,[4] Bianca Kollhorst,[4] Andrea Arfe,[5] Silvia Lucchi,[6] Marco Villa,[6] Jordi Castellsague,[7] Susana Perez-Gutthann,[7] Cristina Varas-Lorenzo,[7] Rene Schade,[1] Martijn J. Schuemie,[1] Yvonne Vergouwe,[9] Ewout Steyerberg,[9] Miriam C.J.M. Sturkenboom,[1,8] and Silvana A. Romio.[1,5] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands; [3]PHARMO Institute, Utrecht, The Netherlands; [4]Leibniz Institute of Prevention Research and Epidemiology, Bremen, Germany; [5]University Milano-Bicocca, Milan, Italy; [6]Local Health Authority ASL Cremona, Cremona, Italy; [7]RTI Health Solutions, Barcelona, Spain; [8]Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands; [9]Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands.*

Background: Use of non-steroidal anti-inflammatory drugs (NSAIDs) can increase the risk of upper gastrointestinal complications (UGIC) and cardiovascular (CV) events. However, the risk may differ between individual NSAIDs and subjects. Decision models for selecting the safest NSAID to treat individual patients are not available.

Objectives: The aim of this study was to provide a decision analytic model to guide physicians in the choice of NSAID treatment that would yield the lowest GI and CV risk for individual patients.

Methods: ***Design*****:** We produced a decision model integrating information from (i) a case–control study on individual NSAIDs and UGIC and CV events; (ii) a risk function for patient characteristics associated with UGIC and CV events; and (iii) disutility weights at 4 weeks: 0.54 for UGIC, 0.65 for ischemic stroke (iCVA), 0.63 for acute myocardial infarction (AMI), and 0.29 for heart failure (HF). *Setting*: We used six European healthcare datasources: (IPCI, PHARMO (NL); SISR, OSSIFF (Italy); GePaRD (Germany) and THIN (UK). The datasource specific study period was 1999–2011. *Exposure*: Thirteen NSAIDs were used. *Outcome*: Outcomes were UGIC, iCVA, AMI and HF hospitalizations. *Statistical analysis*: We calculated adjusted odds ratios (ORs) for UGIC and CV events during individual NSAID exposure. A Poisson regression model was used for risk function. A decision tree was used for the decision model.

Results: In the case–control study, 23 411 UGIC, 35 691 iCVA, 68 757 AMI, and 79 876 HF cases were identified among 8.9 million new NSAID users. The lowest risks were seen for use of celecoxib for UGIC (OR = 1.1) and for HF (OR = 1.0), for iCVA for ketoprofen (OR = 0.9) and for AMI for tenoxicam and aceclofenac (OR = 1.0). For all outcomes, ketorolac yielded the highest risks.

In the risk function, for each outcome, age was the most important predictor, followed by a prior history of the event and sex. In the final decision model, over different scenarios, most preferable NSAIDs were aceclofenac and celecoxib; thereafter, nimesulide and ibuprofen. Piroxicam and ketorolac were the least preferable NSAIDs.

Conclusions: The SOS study provided an integrated GI and CV safety decision model for new NSAID users, which may guide physicians in clinical decision making.

63. The Impact of Cardiovascular Risk, Baseline LDL-Cholesterol, Treatment Dose and Adherence on Cost-Effectiveness of Statins in Newly Diagnosed Diabetes Patients

Dianna de Vries, Eelko Hak, and Maarten J. Postma. *PharmacoEpidemiology & PharmacoEconomics, University Groningen, Groningen, The Netherlands.*

Background: Statins have shown to be cost-effective in most diabetes patients. Treatment decisions in patients newly diagnosed with diabetes are primarily based on the cardiovascular risk. The effect of statins is, however, primarily based on the LDL-cholesterol reduction that is achieved, which is directly related to baseline LDL-cholesterol levels.

Objectives: The aim of this study is to determine the impact of cardiovascular risk, baseline LDL-cholesterol levels, treatment dose and adherence on the number needed to treat (NNT) and cost-effectiveness of statin treatment in newly diagnosed diabetes patients.

Methods: A cost-effectiveness analysis was performed using a Markov model with a time horizon of 10 years. Different scenario analyses were performed in which cardiovascular risk, baseline LDL-cholesterol, treatment dose and adherence were varied. For the base case, we evaluated a fully adherent patient on standard-dose statin treatment with a baseline LDL-cholesterol level of 3.5 mmol/l and a 10-year risk for coronary heart disease of 20%. The NNT was calculated next to cost-effectiveness as expressed in costs per quality-adjusted life year from the healthcare payers' perspective.

Results: In the base case, the NNT to prevent one cardiovascular or cerebrovascular event is 13, and the cost-effectiveness is €2793 over a time horizon of 10 years. For a patient with a 10-year cardiovascular risk of 20%, the NNT ranges from 23 for a baseline LDL-cholesterol level of 2.0 mmol/l to 9 for a baseline LDL-cholesterol level of 5.0 mmol/l; correspondingly, cost-effectiveness ranges from €8075 to €662, respectively. When decreasing adherence to 75%, the NNT increases to 18 and cost-effectiveness to €4991. High-dose treatment decreases the NNT to 9 and increases cost-effectiveness to €4106.

Conclusions: When estimating NNT and related cost-effectiveness of statin treatment, both cardiovascular risk and baseline LDL-cholesterol should be taken into account. For example, statin treatment could also be

highly cost-effective with low NNTs when the cardiovascular risk is low but baseline LDL-cholesterol is high.

64. Costs of Generic Medications, and Its Association with Industry Consolidation

Chintan Dave, and Abraham Hartzema. *Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA.*

Background: Numerous organizations have raised concerns regarding the increases in the cost of generic medications over the past few years.

Objectives: The aims of this study were (i) to quantify the increase in the cost of all generic medications over time and (ii) to identify 20 drugs with the highest increases in cost and examine them for signs of industry consolidation.

Methods: MarketScan commercial claims data from January 2008 to July 2013 were utilized for this study. All generic drug claims were included in the study. The Average Wholesale Price (AWP) was standardized for each drug by dividing it by the metric quantity dispensed. The increase in AWP for generic drugs was compared with consumer price index and healthcare inflation. Drugs were classified into five therapeutic groups, which included agents for diabetes, cholesterol, hypertension, analgesia, and oral antibacterials. We identified 20 agents with the highest increases in AWP over the study period and reviewed the generic industry trends for signs of industry consolidation. Furthermore, we examined actual costs incurred by third party and patients as sensitivity analysis.

Results: Over a period of 5.5 years, we examined 71 million patient records and 1 131 118 650 generic prescription claims. Over the study period, the cost of generic medications increased by 47%, implying an average compound percentage growth of 8.1%. The cost of generics increased at a rate twice the rate of healthcare inflation, and well over four times the CPI. Compared with other classes, diabetic drugs recorded the highest increase with an average yearly rate of 11% while analgesics the lowest increase at 1.6%. The costs incurred by third parties and patients saw similar trends. In the subgroup comprising 20 drugs with the highest cost increases, the number of generic manufacturers decreased from an average of 13.9 in 2008 to 5.8 in 2013, implying significant consolidation within the generic industry in that subgroup.

Conclusions: There is strong evidence of sustained and elevated increases in the cost of generic medications over the study period. This is the first study to examine the trends in the cost of generic medications over time, and on a large population.

65. Prospective Benefit-Risk Monitoring of New Drugs for Rapid Assessment of Net Favorability in Electronic Healthcare Data

Joshua J. Gagne,[1] Katsiaryna Bykov,[1] Mehdi Najafzadeh,[1] Niteesh K. Choudhry,[1] Diane Martin,[2] Kristijan H. Kahler,[2] James R. Rogers,[1] and Sebastian Schneeweiss.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.*

Background: To date, approaches to prospective monitoring of new drugs have focused mostly on safety surveillance and very little on comparative effectiveness. Benefit-risk assessment (BRA) methods combine measures of benefits and risks into a single value and may be useful for simultaneously incorporating relative benefits and risks into the same prospective monitoring framework.

Objectives: The aim of this study was to examine BRA methods for prospective monitoring of new drugs in electronic healthcare data.

Methods: Using two databases, we emulated prospective monitoring of three drugs versus comparators (rofecoxib vs. non-selective non-steroidal anti-inflammatory drugs [ns-NSAIDs], prasugrel vs. clopidogrel, and denosumab vs. bisphosphonates) beginning at market entry of each drug of interest and using a sequential propensity score-matched cohort design. We applied four BRA metrics: number needed to treat and number needed to harm (NNT|NNH), incremental net benefit (INB) with maximum acceptable risk, INB with relative-value adjusted life years (RVALYs), and INB with quality-adjusted life years (QALYs). We determined whether and when the bootstrapped 99% confidence interval (CI) for each metric excluded zero, indicating net favorability of one drug over the other.

Results: For rofecoxib, all four metrics yielded a negative value, suggesting net favorability of ns-NSAIDs over rofecoxib, and the 99%CI for all but the NNT|NNH excluded the null during follow-up. For prasugrel, only the 99%CI for INB-QALY excluded the null, but trends in values over time were similar across the four metrics, suggesting overall net favorability of prasugrel versus clopidogrel. The 99% CI for INB-RVALY and INB-QALY excluded the null in the denosumab example, suggesting net favorability of denosumab over bisphosphonates.

Conclusions: Prospective benefit-risk monitoring can be used to determine net favorability of a new drug in electronic healthcare data. In three examples, existing BRA metrics produced qualitatively similar results but differed with respect to alert generation. INB-QALY produced the most conclusive findings across the three examples.

66. Trends in Pharmaceutical Comparative Effectiveness Research in the Medical Literature, 2004–2013

Laura L. Hester, Elizabeth A. Suarez, Jane Der, and M. Alan Brookhart. *Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Comparative effectiveness research (CER) informs stakeholders on the relative benefits and harms of treatments and guides patient-centered decisions. Interest and investment in CER have risen in the past decade, including $1.1 billion provided for CER through the 2009 US American Recovery and Reinvestment Act (ARRA). No research has explored whether the increased focus on CER has changed characteristics of published pharmaceutical intervention studies.

Objectives: The aim of this study was to identify characteristics of and trends in pharmaceutical CER studies published in the medical literature, 2004–2013.

Methods: We identified 2336 studies published in the five highest impact medical journals between 1 January 2004 and 31 December 2013 with at least one intervention meeting the US Food and Drug Administration's definitions for a drug, biologic, or vaccine. Six trained reviewers extracted study data from a 20% random sample (467 articles). After conducting quality control, study characteristics were summarized, and trends were assessed with Cochran–Mantel–Haenszel exact tests.

Results: Among the 467 pharmaceutical articles, 132 (28.3%) compared at least one pharmaceutical intervention with another treatment. The proportion of CER studies did not increase over time ($p = 0.7$). Most CER studies had randomized versus observational designs (86.4% vs. 13.6%). The percent of observational CER studies was not associated with year ($p > 0.9$). Among CER studies, 53.0% had industry funding and 26.5% had US government funding. The proportion of US government-funded CER studies was similar before and after ARRA funds were awarded in 2009 (48.5% vs. 51.5%). Patient-reported outcomes (PROs) were used less in CER versus non-CER studies (28.8% vs. 33.1%). The proportion of studies with PROs increased over time, especially among industry-funded ($p < 0.01$) and placebo-controlled ($p = 0.03$) studies.

Conclusions: Despite growing interest and investment in CER over the past decade, there were no notable changes in the proportion of pharmaceutical CER studies published in high-impact medical journals. Use of PROs has increased, suggesting a greater focus on patient-centered research in recent years.

67. Testosterone and Acute Cerebro- and Cardiovascular Adverse Events: A Self-controlled Analysis

J. Bradley Layton,[1] Dongmei Li,[1] Julie L. Sharpless,[2] Christoph R. Meier,[3] Byeong Y. Choi,[4] Til Stürmer,[1] and M. Alan Brookhart.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]Pharmaceutical Sciences, The University of Basel, Basel, Switzerland; [4]Department of Biostatistics, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Men frequently use prescription testosterone products briefly and intermittently, which creates intermittent periods of exposure and non-exposure within individuals. Testosterone is known to affect blood clotting and polycythemia, and while the literature is mixed, some studies have suggested testosterone use may increase short-term risk of cardiovascular events and stroke.

Objectives: The aim of this study was to determine the association between testosterone receipt and short-term time on treatment, and the risk of developing acute cardiovascular and cerebrovascular outcomes.

Methods: We identified adult men hospitalized with myocardial infarction (MI) or stroke in US commercial claims (MarketScan) or Medicare (MC) databases, and we characterized their testosterone utilization from pharmacy dispensing claims or in-office procedure codes. We conducted a self-controlled case series (SCCS) analysis comparing the risk of acute MI or stroke events during time on treatment to time off treatment within individuals. We also conducted a case–crossover (CC) analysis comparing injection testosterone exposure in the 7 days prior to an outcome event to control windows in the past to measure the immediate impact of post-injection spikes in serum testosterone levels.

Results: For the SCCS, we identified 279 787 men with events from MarketScan and 86 760 from MC (with 5.8% and 2.0% with some testosterone use, respectively). For the CC, we identified 284 218 men with events from MarketScan and 91 348 from Medicare. SCCS analysis showed elevated risks during the periods on treatment compared with periods off treatment: MarketScan, MI RR = 1.20 (95%CI: 1.12–1.29), stroke RR = 1.07 (1.00–1.15); MC, MI RR = 1.36 (1.09–1.71), stroke RR = 1.33 (1.09–1.62). CC analysis of injection demonstrated an increased risk of adverse events in the immediate post-injection period for older patients: MarketScan, Composite RR = 0.97 (0.84, 1.11); MC, Composite RR = 1.41 (1.04, 1.92).

Conclusions: Testosterone treatment may increase short-term risk of acute cardiovascular and cerebrovascular events in adult and elderly men while on treatment, particularly testosterone injections in elderly men.

68. Increased Risk of Non-fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle,[1] Sander Greenland,[2] Gregory K. Ridgeway,[3] John L. Adams,[4] and Robert N. Hoover.[5] *[1]Consolidated Research Inc., Los Angeles, CA, USA; [2]Department of Epidemiology and Department of Statistics, University of California, Los Angeles, Los Angeles, CA, USA; [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.*

Background: An association between testosterone therapy (TT) and cardiovascular disease has been reported, and TT use is increasing rapidly.

Objectives: The aim of this study was to examine the association between testosterone treatment and risk of myocardial infarction in men by age and history of heart disease.

Methods: We conducted a cohort study of the risk of acute non-fatal myocardial infarction (MI) following an initial TT prescription ($N = 55\,593$) in a large health-care database. We compared the incidence rate of MI in the 90 days following the initial prescription (post-prescription interval) with the rate in the 1 year prior to the initial prescription (pre-prescription interval) (post/pre). We also compared post/pre rates in a cohort of men prescribed phosphodiesterase type 5 inhibitors (PDE5I; sildenafil or tadalafil, $N = 167\,279$) and compared TT prescription post/pre rates with the PDE5I post/pre rates, adjusting for potential confounders using doubly robust estimation.

Results: In all subjects, the post-/pre-prescription rate ratio (RR) for TT prescription was 1.36 (1.03, 1.81). In men aged 65 years and older, the RR was 2.19 (1.27, 3.77) for TT prescription and 1.15 (0.83, 1.59) for PDE5I, and the ratio of the rate ratios (RRR) for TT prescription relative to PDE5I was 1.90 (1.04, 3.49). The RR for TT prescription increased with age from 0.95 (0.54, 1.67) for men under age 55 years to 3.43 (1.54, 7.56) for those aged ≥75 years (ptrend = 0.03), while no trend was seen for PDE5I (ptrend = 0.18). In men under age 65 years, excess risk was confined to those with a prior history of heart disease, with RRs of 2.90 (1.49, 5.62) for TT prescription and 1.40 (0.91, 2.14) for PDE5I, and a RRR of 2.07 (1.05, 4.11).

Conclusions: In older men, and in younger men with pre-existing diagnosed heart disease, the risk of MI following initiation of TT prescription is substantially increased.

69. Cardiovascular Safety of Testosterone Replacement Therapy in Androgen Deficient Males

T. Craig Cheetham,[1] JaeJin An[2], Fang Niu,[3] Steve Jacobsen,[1] and Stephen VanDenEeden.[4] *[1]Department of Research & Evaluation, Southern California Permanente Medical Group, Pasadena, CA, USA; [2]Department of Pharmacy Practice, Western University,*

Pomona, CA, USA; [3]Drug Information Service, Kaiser Permanente Southern California, Downey, CA, USA; [4]Division of Research, The Permanente Medical Group, Oakland, CA, USA.

Background: There has been a growing trend in the USA to treat aging men with testosterone replacement therapy (TRT). However, TRT has become controversial following reports of adverse cardiovascular (CV) events in treated patients.

Objectives: The aim of this study was to determine the risk of adverse CV events in androgen-deficient men receiving TRT.

Methods: A retrospective cohort study of androgen-deficient men was conducted within an integrated healthcare delivery system. Between 1 January 1999 and 31 December 2010, male patients ≥40 years of age entered the cohort based on evidence of androgen deficiency, using diagnosis codes and/or low serum testosterone values (<300 ng/dL). Eligible men were divided into TRT and non-TRT cohorts and followed until 31 December 2011. The primary outcome of interest was a composite of CV events (myocardial infarction, coronary intervention procedures, sudden cardiac death and stroke). Data were collected on baseline demographic characteristics, CV risk factors and disease comorbidity score. Analyses employed a Cox proportional hazards model using inverse probability treatment weights to adjust for treatment selection bias.

Results: A total of 70 356 patients met eligibility requirements for the study (13 834 in the TRT and 56 522 in the non-TRT cohorts). The two cohorts were balanced with respect to baseline characteristics. The age distribution was as follows: 40–55 years = 41.9%, 56–65 years = 29.9% and >65 years = 28.1%. The majority of individuals (97%) had testosterone levels <300 ng/dL at baseline. A total of 6882 CV events occurred during a median 3.5 years of follow-up (1111 in the TRT and 5771 in the non-TRT cohorts). Unadjusted event rates were 79 per 1000 person-years in the TRT cohort and 102 per 1000 person-years in the non-TRT cohort. The adjusted hazard ratio for CV events associated with TRT was 0.68 (95%CI, 0.62–0.75).

Conclusions: In this study of androgen-deficient men, TRT was not associated with an increase in adverse CV events. While residual confounding may explain some of the inverse association, these data suggest that CV events may not weigh as heavily in the risk/benefit comparison.

70. Assessment of the Association Between the Use of Testosterone Replacement Therapy (TRT) and the Increased Risk of Venous Thrombotic Events (VTE) Among TRT Treated and Untreated Hypogonadal Men

Hu Li, Nancy L. Ostrowski, Karin Benoit, Wei Wang, and Stephen Motsko *Eli Lilly, Indianapolis, IN, USA.*

Background: To date, limited information exists as to whether testosterone replacement therapy (TRT) is associated with risk of venous thrombotic events (VTE).

Objectives: The aim of this study was to investigate whether an association exists between TRT and VTE in hypogonadal men using Truven databases.

Methods: Adult men with a hypogonadal condition were obtained (≥12 months enrollment) with no VTE diagnosis at baseline. In the retrospective cohort analysis, TRT-treated patients were matched to untreated patients based on 1:1 propensity score to ensure comparability. Index date was defined as the first TRT prescription date or was randomly assigned to untreated patients based on the distribution of treated patients. In nested case–control analyses, VTE cases were 1:4 matched to controls based on age and calendar year. The event date was the VTE diagnosis date. The outcome was defined as primarily incident idiopathic VTE; exposure was assessed as primarily any TRT use and by different administration routes. Cox regression and conditional logistic regression were used in cohort and nested case–control analyses, respectively, to assess hazard ratios (HRs) and odds ratios (ORs). Sensitivity analyses were also performed.

Results: A total of 533 223 hypogonadal men met study inclusion criteria. After matching, 102 650 TRT-treated and 102 650 untreated patients were obtained. Retrospective cohort analysis revealed an HR for idiopathic VTE of 1.08 for all TRT-treated (95%CI: 0.91, 1.27; $p = 0.378$), 1.07 for topical/gel TRT treated (95%CI: 0.88,1.29; $p = 0.496$), and 1.32 for injectable TRT-treated patients (95%CI: 0.89,1.96; $p = 0.164$). Age stratification (≤65 vs. >65 years) revealed similar non-significant results. Nested case–control analyses of 2785 VTE cases and 11 119 controls revealed similar, non-significant findings. The OR for current TRT was

1.02 (95%CI: 0.92, 1.13; $p=0.702$) and for past TRT 0.92 (95%CI: 0.82, 1.03; $p=0.145$). Similar, nonsignificant findings were observed with age and TRT administration route stratification.

Conclusions: The study results do not support an association between exogenous TRT in hypogonadal men and an increased risk of VTE.

71. Cardiovascular Safety in Users of Different Combined Oral Contraceptives—Final Results from the INAS-SCORE Study

Kristina Bardenheuer, Klaas Heinemann, Thai Do Minh,[1] and Christian Franke. *ZEG—Berlin Center for Epidemiology and Health Research, Berlin, Germany.*

Background: A new combined oral contraceptive (COC) with a 26-day regiment containing estradiol valerate and dienogest, known as Qlaira (and Natazia in the USA), was launched in 2009. However, it is unknown whether this new regimen and combination has an impact on the cardiovascular risk associated with the use of COCs.

Objectives: Risks of short-term and long-term use are compared between the newly launched and established COCs.

Methods: The "International Active Surveillance Study—Safety of Contraceptives: Role of Estrogens" is being requested by the Medicines Evaluation Board. It is a large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of the study participants. It is conducted in the USA as well as in Austria, France, Germany, Italy, UK, Poland and Sweden.

Women being prescribed a new COC (either first-time user or switcher) are recruited by a network of prescribing physicians. Every 6 months during the first 2 years and yearly thereafter, the woman is contacted and asked amongst other about hormonal contraceptive use and serious adverse events. All self-reported clinical outcomes of interest are validated by healthcare professionals. Main clinical outcomes of interest are venous thromboembolism and arterial thromboembolism. All analyses make allowance for confounding, using multivariate techniques such as Cox regression models.

Results: The analysis is based on 98 234 women-years (WY) of observation and 72 160 WY of OC exposure. Overall, 57 venous thrombotic events (VTEs) and 15 arterial thrombotic events (ATEs) have occurred. For Qlaira, the VTE incidence is 6.4/10 000 WY, and for Other COCs, 7.5/10 000 WY. The crude HR for Qlaira versus Other COCs is 0.8 (95%CI: 0.4–1.8). Adjustment for age, BMI, duration of current OC use and family history of VTE lead to an adjusted HR of 0.5 (95%CI: 0.2–1.6). ATE incidences were very low with 0.8 ATE/10 000 WY for Qlaira and 2.2 ATE/10 000 WY for Other COCs. Final results will be shown at International Society for Pharmacoepidemiology.

Conclusions: The results do not suggest a higher VTE or ATE risk of Qlaira users compared with users of Other COCs in a study population that is representative of actual users.

72. Drospirenone-Containing Combined Oral Contraceptives and the Risk of Arterial Thrombosis: A Population-Based Nested Case–Control Study

Kristian B. Filion,[1] Maria Eberg,[1] Lawrence Joseph,[2] Mark J. Eisenberg,[3] Haim A. Abenhaim,[4] and Samy Suissa.[1] *[1]Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada; [2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [3]Center for Clinical Epidemiology and Division of Cardiology, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada; [4]Center for Clinical Epidemiology and Department of Obstetrics and Gynecology, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada.*

Background: While much attention has focused on the risk of venous thrombosis with drospirenone-containing combined oral contraceptives (COCs) compared with that of levonorgestrel-containing COCs, their relative effects on the risk of arterial thrombosis (AT) remain understudied.

Objectives: The aim of this study was to compare the rate of AT of drospirenone-containing COCs with that of levonorgestrel-containing COCs.

Methods: We conducted a nested case–control analysis of a population-based cohort using the UK's Clinical Practice Research Datalink (CPRD). Cohort entry was defined by a prescription for drospirenone-containing or levonorgestrel-containing COCs. Cases

were defined by a diagnosis of AT, including myocardial infarction and stroke. For each case, up to 10 controls were matched on age, year of cohort entry, year of CPRD registration, COC user type (first time, new, or prevalent users), total duration of COC use, total duration of non-COC use, duration of exposure use, and duration of follow-up. High-dimensional propensity scores were included in our conditional logistic models to reduce residual confounding.

Results: Our cohort included 339 743 women followed up over a mean of 4.4 years, during which a total of 228 AT cases occurred (37 myocardial infarctions, 170 strokes, and 21 other ATs; overall rate = 1.5 events per 10 000 person-years [PYs]). After adjustment, current use of drospirenone-containing COCs was not associated with the rate of AT compared with current use of levonorgestrel-containing COCs, though 95%CIs were wide (OR = 0.89, 95%CI = 0.35, 2.28, corresponding to a rate difference = −0.16 events per 10 000 PYs, 95% = −0.97, 1.78).

Conclusions: The overall rate of AT in this population is low, and we found no evidence of a difference in the rate of AT with drospirenone-containing COCs relative to levonorgestrel-containing COCs. Owing to the limited number of events in this population, there remains a need for further studies examining this potential adverse drug effect.

73. From Fantasy to Reality: Embedding Pragmatic Trials into Routine Clinical Care

Robert F. Reynolds,[1] Anne Trontell,[2] Zhanna Jumadilova,[3] Louis Fiore,[4] and Liam Smeeth.[5] *[1]Epidemiology, Pfizer, New York, USA; [2]Patient-Centered Outcomes Research Institute, Washington, DC, USA; [3]Clinical Sciences, Pfizer, New York, USA; [4]Massachesetts Veterans Epidemiology Research and Information Center (MAVERIC), Boston, MA, USA; [5]Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK.*

Background: Pragmatic trials are randomized studies characterized by their recruitment of physicians and patients from diverse clinical practice settings, broad inclusion criteria for study participation, assessment of clinically relevant outcomes and observational follow-up. The design allows epidemiologists to address concerns about selection bias in nonrandomized observational studies while assessing the effectiveness of medications as they are used in 'real-world' clinical practice. There is growing recognition of the need for comparative effectiveness findings from pragmatic trials.

Objectives: The methodological and operational challenges of conducting pragmatic trials embedded in routine data collection will be examined. Examples of trials that have been successfully conducted in Clinical Practice Research Datalink, the Veterans Affairs, and US electronic health records (EHRs) will illustrate the key points followed by a panel Q&A session with participation from the audience.

Description: *Pragmatic Trials in Europe Using Electronic Health Records and Disease Registries*

This talk will review the challenges and opportunities in using EHRs and disease registries for pragmatic trials in Europe.

Facilitating the Rapid Conduct of Pragmatic Clinical Trials: A "CHOICE" Experience

This talk will describe the challenges and lessons learned from 12 pragmatic studies funded in 2010 by Agency for Healthcare Research and Quality, the Clinical and Health Outcomes in Comparative Effectiveness Program.

Implementing Pragmatic Trials in Electronic Healthcare Data: Lessons Learned

This presentation will examine two pragmatic trials assessing the effectiveness of non-medicinal interventions in electronic healthcare data sources. The talk will cover challenges related to utilizing electronic healthcare data in the setting of a pragmatic study.

The Department of Veterans Affairs Point of Care Clinical and Precision Oncology Programs

This talk will review strategies taken by the VA to embed research activities in the clinical care ecosystem. Partnering with clinical entities reduces the cost and increases the clinical relevance of the research. Two pragmatic point-of-care clinical trials will be reviewed to highlight cultural, technical, and regulatory issues of this approach.

74. An International Working Collaborative to Examine Global Drug Utilisation: Opioid Use and Misuse

Gillian Caughey,[1] Katja Taxis,[2] Bjorn Wettermark,[3] Ingrid Sketris,[4] Li-Chia Chen,[5] and Lisa Pont.[6] *[1]Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia; [2]Department of*

Pharmacy, University of Groningen, Groningen, The Netherlands; [3]Center for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden; [4]College of Pharmacy, Dalhousie University, Halifax, NS, Canada; [5]Division for Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, Nottingham, UK; [6]Australian Institute for Health Innovation, Macquarie University, Sydney, NSW, Australia.

Background: Following on from the Drug Utilisation/Health Services Research SIG meeting in Taiwan 2014, there was strong interest to develop an international drug utilisation study collaborative, open to all International Society for Pharmacoepidemiology members. Opioid use is increasing in many countries, and the appropriateness of prescribing these medications long term is under increasing scrutiny, owing to increased risk of dependence and abuse, potentially leading to overdose and even death. Using opioid utilisation as the initial study exemplar, this global comparison will identify key factors that influence utilisation and quality use of medicines to facilitate the development of interventions to improve appropriate prescribing.

Objectives: The aim of this study was to develop an international working group to undertake studies to examine global drug utilisation, using opioid utilisation as the initial study focus.

Description: This Drug Utilisation/Health Services Research SIG-endorsed workshop will provide an interactive forum to develop a multi-country standardised study framework and design, to examine and evaluate the global utilisation of opioids. The workshop will be divided into two parts. The first will provide an overview of what is known about opioid utilisation around the world and the various factors influencing utilisation, including (i) prescribing regulations and clinical guidelines, (ii) prescriber and patient attitudes and (iii) health policy and pricing (30 minutes). In the second part, a small overview of potential methodological approaches, study design and use of available data sources will be presented (10 minutes). This will be followed by an interactive discussion with participants led by the study panelists (50 minutes) to determine an appropriate study design, a common data model of key variables applicable for each country dataset, study outcome variables and analysis methods. The use of opioids in specific sub-sets of patients including those with cancer, non-cancer pain and older adults will be explored. The feasibility and challenges associated in undertaking this international collaborative will also be discussed.

75. Technical and Governance Challenges in Pharmacoepidemiology Data Integration

Kevin Haynes,[1] Richard Platt,[2] Katerine Yih,[2] Susan E. Andrade,[3] and Sangwee D. Toh.[2] *[1]Government & Academic Research, HealthCore, Inc, Wilmington, DE, USA; [2]Department of Population Medicine, Harvard Medical School, Boston, MA, USA; [3]Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester, MA, USA.*

Background: There is a critical need to link data resources to address complex clinical research objectives. There are technical and governance challenges to overcome in linkage of pharmacoepidemiology resources.

Objectives: The workshop will review technical and governance challenges in linking pharmacoepidemiology data resources and propose analytic techniques for privacy-preserving analytic and data-sharing methods. The workshop will provide an overview for data linkage across multiple data resources, including administrative claims data with electronic medical records. Two real-world examples will highlight the technical and governance issues experienced. Finally, an analytic technique for vertical data integration while preserving patient privacy will be presented. Researchers involved or wanting additional expertise in the ability to integrate pharmacoepidemiology data would benefit from workshop participation. Additionally, the workshop is seeking ISPE membership discussion and feedback on data integration.

Description: Kevin Haynes will moderate and facilitate membership discussion on pharmacoepidemiology data linkage (5 minutes). Richard Platt will provide compelling evidence for the need to integrate data resources highlighting current needs for patient-oriented comparative effectiveness research within PCORnet and the ability to conduct active safety surveillance within the Sentinel system (10 minutes). Katherine Yih will provide an example of data integration conducted by the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program to link immunization registries with administrative claims data, highlighting the technical and governance challenges (15 minutes). Susan Andrade will provide an example of data integration conducted by PRISM

to link birth certificate data from Vital Events Registries from Departments of Health highlighting the technical and governance challenges (15 minutes). Darren Toh will provide a presentation of vertical data integration as part of privacy-preserving analytic and data-sharing methods for clinical and patient-powered data networks (20 minutes).

ISPE membership discussion of technical and governance challenges experienced in linking databases (25 minutes).

76. Methods to Include Clinical Data Elements when Analyzing Observational Health Care Data Where Missing Data Are Expected

Marsha A. Raebel,[1] Jason Roy,[2] Susan Shetterly,[1] and Joshua J. Gagne.[3] *[1]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA; [2]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.*

Background: Use of clinical data such as laboratory test results is not straightforward because they carry availability and completeness issues reflecting several missing data mechanisms. Inclusion of lab results data in active surveillance analyses without considering the missing data or with applying older analytic techniques can yield markedly biased estimates. Recent approaches to handling missing data such as multiple imputation (MI), MI with predictive mean matching, and MI using chained equations are potentially useful. However, testing the performance of statistical approaches and developing guidance for appropriately including lab results in safety surveillance is critical.

Objectives: The aim of this study was to discuss analytic methods appropriate for use when analyzing cross-sectional and longitudinal observational clinical data, with specific attention to clinical laboratory test results data when missing data are expected. Researchers involved with analyzing large observational databases composed of administrative, clinical, and electronic health record data will benefit by attending this symposium.

Description: During this symposium, we will review the use of laboratory test results in observational multi-site database studies of medical product safety, and the mechanisms and patterns of missing data inherent to such databases. We will discuss considerations when selecting analytic methods and compare the performance of statistical methods for use when analyzing cross-sectional and longitudinal observational healthcare administrative, claims, and clinical data. Specific attention will be paid to lab test results data when missing data are expected and to distributed database environments. We will discuss the application of methods when laboratory test results data are used for different purposes (e.g., confounding adjustment, ascertaining outcomes, cohort identification). Perspective about implications for surveillance systems (e.g., the US Food and Drug Administration Sentinel Program) will be provided.

77. Does the Increasing Specialization of Epidemiologic Societies Ensure the Best Future for Our Profession?

Jennifer L. Lund,[1] Til Sturmer,[1] Timothy L. Lash,[2] John Acquavella,[3] Henrik Støvring,[4] Malcolm Maclure,[5] Francine Laden,[6] Vincent Lo Re,[7] Martha Werler,[8] and Susan Sacks.[9] *[1]Department of Epidemiology, Gillings School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [3]Private Consultant, Prescott, AZ, USA; [4]Department of Public Health, Department of Biostatistics, Aarhus University, Aarhus, Denmark; [5]Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada; [6]Department of Environmental Health, Department of Epidemiology, Harvard University, TH Chan School of Public Health, Boston, MA, USA; [7]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA; [8]Department of Epidemiology, Boston University, Boston, MA, USA; [9]Private Consultant, New York, NY, USA.*

Background: Over time, epidemiologic societies have become increasingly specialized, organizing their membership around geography, disease state or content area. This symposium will bring together past and present leaders representing the Society for Epidemiologic Research (SER), the International Epidemiologic Association, European Federation (IEA-EEF), the American College of Epidemiology (ACE) and the International Society for Pharmacoepidemiology (ISPE) to discuss the implications of

increasing specialization within our field and to develop consensus on how ISPE can work with other societies to promote common goals and values.

Objectives: The aims of this study were to provide a broad overview of the some of the largest general epidemiologic societies and to learn about the specific challenges facing these organizations and about new initiatives to expand and retain members. We will engage the audience in a discussion about the relations between epidemiologic societies and ISPE, how we can learn from each other's experiences and work together to achieve common goals.

Description: This symposium, sponsored by the ISPE Membership Committee, will start with the moderator providing an overview of the goals for the session and an introduction of the invited speakers. Each of the four society leadership presenters will then have 10 minutes to describe their organization and address specific challenges faced by their society. Following the individual presentations, the invited speakers will be joined on stage by five additional panelists representing different epidemiology societies and academic, industry and government perspectives for an open 35-minute discussion with the audience about the presentations. The final 10 minutes will be used to summarize the discussion and develop consensus action items to present to the various society leadership committees.

Speakers: Timothy L. Lash (SER), Til Stürmer (ISPE), John Acquavella (ACE), and Henrik Støvring (IEA-EEF)

Panelists: Malcolm Maclure (ISPE, Government), Francine Laden (ISEE, Academic), Vincent Lo Re (ISPE, Membership Committee, Academic), Martha Werler (SPER, Academic (tentative)), and Susan Sacks (SER, ISPE, Industry)

78. Data Driven Regulatory Science

Marie L. De Bruin,[1] Haggar H. Ampadu,[2] Jarno Hoekman,[1] Xavier Kurz,[3] Hubert G. M. Leufkens,[1] Shohko Sekine,[4,5] and Gerald Dal Pan.[4] *[1]WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht University, Utrecht, The Netherlands; [2]The WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Accra, Ghana; [3]European Medicines Agency, London, UK; [4]Center for Drug Evaluation and Research, FDA, Silver Spring, MD, USA; [5]Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan.*

Background: Drug regulatory science closely relates to pharmacoepidemiology, particularly where epidemiologic methods are used to derive empirical evidence on the outcomes and implications of drug regulation.

Objectives: In this symposium, we will present the results from recent regulatory science studies on the functioning of post-marketing surveillance systems.

Description: After a short introduction of the scientific field and methods applied to evaluate pharmacovigilance systems, results from four recently performed studies will be presented. The studies cover different aspects from the pharmacovigilance system in different continents:

(1) Predictors of successful pharmacovigilance systems in Africa: determinants of ADR reporting in African countries (Hilda Ampadu)
(2) FDAAA mandated 18 months, 10 000 patient reviews: experiences with the first cohort of newly approved products in the USA since 2007 (Shohko Sekine)
(3) Characteristics and follow-up of post-marketing obligations of medicinal products with a conditional marketing authorization in Europe, 2006–2014 (Jarno Hoekman)
(4) The role of registries in European post-marketing surveillance, a retrospective analysis of centrally approved products, 2005–2013 (Xavier Kurz)

A multidisciplinary panel will provide their views and results of the studies. Implications for policy and further research will be discussed with panelists and the broader audience. Three different angles of focus will be chosen.

The academic perspective: What are the implications for data collection and methodologies?

The regulatory perspective: What are the implications for design and enforcement of post-marketing obligations?

The pharmacovigilance perspective: What are the implications for how to organize to post-marketing surveillance in practice?

79. Human–Algorithm Interaction to Define Variables from Free-Text Notes in Electronic Health Records—Introduction and Examples

David D. Dore,[1] Anthony P. Nunes,[1] Charles Yee,[2] and Alexander M Walker.[3] *[1]Optum Epidemiology, Waltham, MA, USA; [2]Humedica, Optum Company, Boston, MA, USA; [3]WHISCON, Newton, MA, USA*

Background: There is information latent within the rich sequence of data contained in electronic health records (EHRs) that is challenging to classify with pre-specified operational definitions. Interaction between humans and analytic algorithms can improve validity.

Objectives: The objective of this session is to demonstrate data-interactive methods for defining study variables within EHRs, with a focus on free-text clinical notes.

Description: Using examples from recent work, we will introduce the paradigm of iterative empirical structuring of variables and methods for extracting concepts from free-text clinical notes via natural language processing. Examples that highlight the difficulty of predicting patterns of data that represent variables of interest will be included. The first of three worked examples will be a comparison of free text and structured variables for identifying hypoglycemia, including discussion of a free-text algorithm and its validation. In the second example, we will discuss the feasibility of classifying binge eating disorder via clinical notes and distinguishing it from other binge eating behaviors. The third example will illustrate supervised training to create an algorithm that applies clinical expertise to identify acute liver dysfunction among persons with inflammatory bowel disease. Finally, we will summarize methodological lessons from the examples and discuss the implications of the proposed methods for epidemiologic work with "big data."

Proposed Agenda:

(1) Introduction and Motivation—Dr. Dore (5 minutes)
(2) Overview of Natural Language Processing—Dr. Yee (15 minutes)
(3) Iterative Empirical Structuring of Variables within EHRs—Dr. Walker (10 minutes)
(4) Worked Example: Free-Text and Structured Variables to Identify Hypoglycemia—Dr. Nunes (10–15 minutes)
(5) Worked Example: Free-Text Classification of Binge Eating—Dr. Dore (10–15 minutes)
(6) Worked Example: Supervised Training for Acute Liver Disease—Dr. Walker (15–20 minutes)
(7) Summary and Panel Discussion with Audience—All Presenters, Led by Dr. Walker (10 minutes)

80. Risk of Non-melanoma Skin Cancer Recurrence with the Use of Immunosuppressant and Biologic Agents in Autoimmune Disease

Frank I. Scott,[1,2] Ronac Mamtani,[2,3] Colleen M. Brensinger,[2,4] Kevin Haynes,[2] Zelma C. Chiesa-Fuxench,[5] Jie Zhang,[6] Lang Chen,[7] Fenglong Xie,[7] Huifeng Yun,[6] Mark T. Osterman,[1,2] Timothy Beukelman,[6] David J. Margolis,[2,5] Jeffrey R. Curtis,[6,7] and James D. Lewis.[1,2] *[1]Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [4]Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [6]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA; [7]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA.*

Background: Immune dysfunction underlies the pathogenesis of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Immunosuppressive therapies have become the standard for treating RA and IBD. Immunosuppression is also believed to be a risk factor for non-melanoma skin cancer (NMSC), particularly squamous cell tumors. For patients with a history of NMSC, there are limited data on the impact of these drugs on the risk of NMSC recurrence.

Objectives: The aim of this study was to determine the relative hazard of a second NMSC in patients with RA or IBD who use methotrexate, anti-tumor necrosis factor (anti-TNF) therapy, or thiopurines after an initial NMSC.

Methods: We performed a retrospective cohort study of adult Medicare beneficiaries with RA or IBD from 2006 to 2012. Exposure to methotrexate, thiopurines, anti-TNFs, sulfasalazine, hydroxychloroquine, abatacept, or rituximab was assessed after the incident NMSC surgery. The primary outcome in Cox regression models was a second NMSC.

Results: Among 9460 individuals (6841 with RA and 2788 with IBD), the incidence rate of second NMSC per 1000 person-years was 58.2 (95%CI, 54.5– 62.1) and 58.9 (53.2–65.2) in RA and IBD, respectively. Among RA patients, methotrexate used in conjunction with other medications was associated with an increased risk of second NMSC (HR 1.60, 95%CI

1.08–2.37). Adjusted for other medications, the risk of NMSC increased with >1 year of methotrexate use (HR 1.24, 95%CI 1.04–1.48). Compared with methotrexate alone, addition of anti-TNF drugs was statistically significantly associated with risk of NMSC (HR 1.49, 95%CI 1.03–2.16). Abatacept and rituximab were not associated with increased NMSC risk. The HRs for more than 1 year of thiopurine and anti-TNF use for IBD were 1.49 (95%CI 0.98–2.27) and 1.36 (95%CI 0.76–2.44), respectively.

Conclusions: Methotrexate use is associated with an increased risk of second NMSC. Anti-TNF use may increase the risk of second NMSC when used with methotrexate for RA. Whether thiopurine and/or anti-TNF use in IBD increases the risk of second NMSC is uncertain; although the HRs were similar to methotrexate and anti-TNF use in RA.

81. Active Surveillance of Skin Toxicities Through Web-Based Patient-Reported (PRO) Toxicity Reporting Tool in Outpatient Cancer Patients on EGFR Tyrosine Kinase Inhibitors (TKI): A Feasibility Study

Tian Qi Wang,[1] Hagit Bergman,[1] Catherine M. Brown,[1] Ashlee Vennettilli,[1] Devalben Patel,[1] Jack T. Seki,[2] Andrea Perez-Cosio,[1] Doris Howell,[1] and Geoffrey Liu.[1] *[1]Research, Princess Margaret Cancer Center, Toronto, ON, Canada; [2]Inpatient Pharmacy, Princess Margaret Cancer Center, Toronto, ON, Canada.*

Background: Novel methods of collecting highly prevalent skin toxicities involving epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) can improve efficiency of phase IV studies, and there has been a recent trend towards patient-reported toxicities.

Objectives: The aim of this study was to evaluate the feasibility of using a patient-reported outcome (PRO) for skin toxicities self-administered through a website.

Methods: This cross-sectional study of 58 adult cancer outpatients who were undergoing treatment with any of the five selected EGFR inhibitors (erlotinib, afatinib, gefitinib, panitumumab, and cetuximab) focused on capturing skin toxicities using a web-based tool in the outpatient oncology clinics at Princess Margaret Cancer Centre (Toronto, Canada). Blinded assessments by physicians were compared with the PRO-tool. A total of 36 blinded skin toxicity assessments were collected simultaneously from patients and physicians.

Results: Very few patients had problems with understanding or using the PRO-tool. Problems that did occur were minor and resolved upon explanation by a researcher. Representative photographs of papulopustular rashes in the PRO-tool were found to be helpful in determining the rash severity, with 16 patients reporting none, 14 mild, 3 moderate, and 3 severe. In contrast, physicians identified 20 patients with no papulopustular rash, 11 with mild, 5 moderate, and 0 severe. Physician assessment also indicated 16 patients with grade 1 skin toxicity, 7 with grade 2, and 0 with grade 3/4. Concordance between none/0, mild/1, moderate/2, and severe/3 rash was seen in 56% of cases; 39% had a discrepancy between adjacent categories. Five percent had a discrepancy of non-adjacent categories.

Conclusions: Skin toxicities were easily captured and found to correlate well with physician assessments. Administration of this web-based PRO-tool may be a useful adjunctive instrument in phase IV trials of skin toxicities but cannot replace the standard physician-reporting tools.

82. Patterns of Granulocyte Colony-Stimulating Factor Use Among Older Women with Breast Cancer: An Analysis of SEER-Medicare Linked Data, 2001–2009

Wan-Ju Lee,[1] Stephen M. Schwartz,[2] and Gregory S. Calip.[1] *[1]Department of Pharmacy Systems, Outcomes and Policy, University of Illinois at Chicago, Chicago, IL, USA; [2]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.*

Background: Granulocyte-colony stimulating factors (G-CSF), including filgrastim and pegfilgrastim, are increasingly used for prevention of infectious complications with chemotherapy-related neutropenia in breast cancer. However, prescribing patterns of costly G-CSF and cytotoxic regimens that predispose their use among older women are not well described.

Objectives: The aim of this study was to illustrate prescribing patterns and identify clinical factors and treatments associated with filgrastim and pegfilgrastim use in an elderly population with breast cancer.

Methods: This was a retrospective cohort study of women aged ≥65 years, with incident stage I–III breast cancer from the Surveillance, Epidemiology and End Results–Medicare linked database between 2001 and 2009. Frequency of G-CSF use among women treated with adjuvant chemotherapy was examined. Multivariable logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for G-CSF use in relation to breast cancer characteristics, treatments and Charlson comorbidity scores. We also conducted analyses for use of pegfilgrastim versus filgrastim.

Results: Among 8854 women treated with adjuvant chemotherapy, mean age was 71.9 years and 60.9% - received G-CSF. G-CSF use increased from 33.6% in 2001 to 66.1% in 2009. Black and Hispanic women were less likely to receive G-CSF. G-CSF use was strongly associated with cyclophosphamide-containing (OR = 5.7, 95%CI 4.7–6.9) and platinum-containing (OR = 6.1, 4.7–7.8) regimens and was moderately associated with taxane-containing (OR = 2.6, 2.2–2.9), anthracycline-containing (OR = 1.8, 1.6–2.1), and fluorouracil-containing (OR = 1.2, 1.0–1.5) regimens. Compared with filgrastim, pegfilgrastim use was associated with younger age (65–69 years, OR = 1.3, 1.1–1.6), radiotherapy (OR = 1.2, 1.0–1.5), and taxane-containing (OR = 2.0, 1.6–2.5) and platinum-containing (OR = 1.7, 1.1–2.5) regimens.

Conclusions: G-CSF use, particularly pegfilgrastim, increased significantly over time among older breast cancer patients receiving chemotherapy. Greater pegfilgrastim use was associated with chemotherapy following radiotherapy, in younger elderly women (65–69 years) and with taxane-containing and platinum-containing regimens.

83. Occurrence of Acute Renal Failure (ARF) on the Same Day as Immune Globulin (IG) Product Administrations During 2008–2014

Bola Ekezue,[1] Gayathri Sridhar,[1] Richard Forshee,[2] Nandini Selvam,[1] Dorothy Scott,[2] Steven Anderson,[2] and Mikhail Menis.[2] *[1]GAR, HealthCore Inc, Alexandria, VA, USA; [2]CBER, US Food and Drug Administration, Silver Spring, MD, USA.*

Background: Immune globulin (IG)-related acute renal failure (ARF) is a rare but serious adverse event(s) that can occur following IG use.

Objectives: The aim of this study was to assess occurrence of ARF on the same day as IG product administration among IG product users during the 2008–2014 study period.

Methods: A retrospective cohort study was conducted using health insurance claims from the HealthCore Integrated Research Database. The cohort included individuals exposed to intravenous and subcutaneous IG products from January 2008 through May 2014. IG product exposures were identified by Healthcare Common Procedure Coding System codes. ARF was ascertained based on the presence of ICD-9-CM diagnosis codes for acute renal failure. Unadjusted same-day ARF rates (per 1000 persons exposed) were estimated overall, and by year, age, sex, and specific IG products. Multivariable analyses are planned to control for confounding and assess potential risk factors.

Results: Of 20 440 persons exposed, 163 (7.97 per 1000 persons) had a recorded diagnosis of ARF on the same-day as IG exposure. The annual rates (per 1000 persons exposed) for the 2008–2014 study period were 3.11, 4.30, 6.04, 4.19, 3.91, 2.69, and 2.84, respectively. When stratified by age groups, same-day ARF rates (per 1000) were 3.41 for under 15 years of age, 7.70 for 15 to 44 years, 9.21 for 45 to 64 years, and 7.95 for 65 years and older. The ARF rates (per 1000) varied by sex, with 6.60 for women and 9.55 for men. The non-zero IG product specific same-day ARF rates (per 1000) ranged from 1.92 to 16.97.

Conclusions: The study showed variation in the risk of ARF among IG users by year, age, sex, and different IG products administered. The study results suggested higher risk of the same-day ARF among men and for person ages 45 years and over. Variations in ARF occurrence may also be explained by product dosages, rates and routes of administration, manufacturing processes, and underlying health conditions that will be further assessed in multivariable analyses.

84. Occurrence of Hemolytic Reactions (HRs) on the Same Day as Immune Globulin (IG) Product Administrations During 2008–2014

Bola Ekezue,[1] Gayathri Sridhar,[1] Richard Forshee,[2] Nandini Selvam,[1] Steven Anderson,[2] and Mikhail Menis.[2] *[1]Government and Academic Research, HealthCore Inc, Alexandria, VA, USA; [2]CBER, US Food and Drug Administration, Silver Spring, MD, USA.*

Background: Hemolytic reactions (HRs) are rare but serious adverse events that can occur following immune globulin (IG) use.

Objectives: The aims of this study were to assess the risk of same-day HR occurrence by different IG products and identify potential recipient risk factors during the 2008–2014 study period.

Methods: A retrospective cohort study was conducted using administrative claims data from HealthCore Integrated Research Database. The cohort included individuals exposed to intravenous and subcutaneous IG products from January 2008 through May 2014. IG product exposures were identified by Healthcare Common Procedure Coding System procedure codes, and HRs were assessed as a composite outcome based on recorded ICD-9-CM diagnosis codes. Unadjusted analyses were conducted to assess same-day HR rates per 1000 persons exposed overall, by age, sex, and different IG products. Multivariable logistic regression analyses were used to estimate the association between IG product exposure and same-day HR occurrence, while controlling for potential confounders.

Results: Of 20 440 persons exposed to IGs, 211 (10.3 per 1000 persons) had claims evidence of HRs on the same day as product administration. The non-zero IG product specific HR rates (per 1000) varied for different IG products, from 1.92 to 17.99. HR rates per 1000 persons exposed were 8.71 (95 of 10 913) for women and 12.18 (116 of 9527) for men. When stratified by age groups, the overall HR rates per 1000 persons exposed were 13.66 for <15 years of age, 7.49 for 15–44 years, 7.72 for 45–64 years, and 16.32 for ≥65 years. The overall multivariable regression analysis showed significantly increased same-day HR risk among IG users ages 65 years and older, with off-label use, and with histories of hemolysis and anemias.

Conclusions: The study findings show that same-day HR rates among IG users may vary by age, sex, and IG products. The study suggests the importance of off-label use, older age, and underlying health conditions in IG-related hemolysis occurrence. Factors such as product dosage, rates of IG administration, and differences in product manufacturing processes may contribute to the study's findings and warrant further investigations.

85. Majority of Patients Do not Store Their Biological Disease Modifying Antirheumatic Drugs Within Recommended Temperature Range

Nicolaas D. Vlieland,[1] Helga Gardarsdottir,[1,2] Marcel L. Bouvy,[2] Antoine C. G. Egberts,[1,2] and Bart J. F. van den Bemt.[3,4] *[1]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands; [2]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands; [3]Department of Pharmacy, Sint Maartenskliniek, Nijmegen, The Netherlands; [4]Department of Pharmacy, Radboud Medical Center, Nijmegen, The Netherlands.*

Background: Proper storage and controlled distribution of biological disease modifying antirheumatic drugs (bDMARDs) are essential to ensure drug quality. Deviations from the manufacturers' Summary of Product Characteristics (SmPC) recommended temperature range (2–8°C) at patients' home may lead to protein aggregation, which has been associated with an increased immunogenicity. This could result in decreased clinical efficacy and increased risk of adverse drug reactions.

Objectives: The aim of this study was to evaluate whether patients' home storage temperatures for bDMARDs comply with SmPC recommended storage temperature range.

Methods: A prospective follow-up study was conducted in eight Dutch outpatient pharmacies from December 2013 till January 2015. Consenting adult patients received their bDMARDs including a validated temperature logger and were instructed to store their packages according to standard label instructions and to return the temperature logger(s) after use. Primary outcome was the proportion of patients that stored their bDMARDs within the SmPC recommended temperature range without excursions longer than 48 hours in total below 2°C or above 8°C. In addition, duration of storage (hours) as well as the proportion of patients storing bDMARDs below 0°C and above 25°C longer than two consecutive hours was assessed.

Results: A total of 338 patients were included of which 278 (82.2%) patients (mean age 52.9 (SD 13.4); 52.0% female) returned their temperature logger(s) to the pharmacy; 79 patients (28.5%) stored their bDMARD within the SmPC recommended temperature range. The proportion of the patients that stored their bDMARD for more than 2 hours' consecutive time below 0°C or above 25°C was respectively 23.8% (median duration: 3.7 hours (interquartile range (IQR) 2.3 hours; range 2.0–1097.1 hours)) and 1.8% (median duration: 11.8 hours (IQR 44.3 hours; range 2.0–384.3 hours)).

Conclusions: The majority of patients do not store their bDMARDs within the SmPC recommended storage temperature range. To what extent moderate and extreme deviations in bDMARD storage temperatures could affect drug quality and influence efficacy and occurrence of adverse drug reactions needs further investigation.

86. Prevalence and Overlap of Asthma Phenotypes in a General Asthma Population

Trung N. Tran,[1] and Christine K. Ward.[2] [1]*Observational Research Center, AstraZeneca, Gaithersburg, MD, USA;* [2]*Translational Medicine, MedImmune, Gaithersburg, MD, USA.*

Background: Atopic, eosinophilic, and T helper cell type 2-high (Th2-high) asthma phenotypes may overlap. Several new biologic therapies targeting specific asthma phenotypes are either available or in development; newer medications may also treat more than one phenotype. Understanding the overlap across asthma phenotypes may be useful in determining treatment guidance, optimization, and overall care.

Objectives: The aim of this study was to describe the prevalence and overlap of atopic, eosinophilic, and Th2-high phenotypes in a general asthma population.

Methods: Data from the annual National Health and Nutrition Examination Survey, among a representative sample of the general US population, were analyzed. Asthma patients were identified based on the participants' self-report. Eosinophilic asthma was defined as a blood eosinophil count ≥300 cells/μL. Atopic asthma was identified as an allergen-specific immunoglobulin E (IgE) level of ≥0.35 IU/mL, for any of the nine tested perennial allergens. Th2-high asthma was defined as total serum IgE ≥100 IU/mL and a blood eosinophil of either ≥100 or ≥200 cells/μL (Corren et al. N Engl J Med 2011;365:1088–1098). The study included only survey years 2005–2006 for which IgE data were collected.

Results: The study included 265 children (aged 6–17 years) and 303 adult (18–64 years) asthma patients; 57% of children and 41% of adults were classified as eosinophilic, 50% and 42% as Th2-high, and 63% and 61% as atopic asthma, respectively. Among those with atopic asthma, 75% of children and 50% of adults were also eosinophilic, and 70% and 60%, respectively, were Th2-high. Among those with Th2-high asthma, 80% of children and 62% of adults were eosinophilic; 38% of children and 23% of adult patients could be classified as eosinophilic, atopic, and Th2-high, simultaneously; 77% of children and 74% of adult asthma belonged to one of these three phenotypes.

Conclusions: A significant overlap exists among eosinophilic, atopic, and Th2-high asthma phenotypes in a general asthma population, especially in children. Future studies need to examine whether an overlap is also present in severe asthma patients who are the likely target of biologics and new asthma therapies.

87. Insulin Treatment and Breast Cancer Risk; A Systematic Review of In Vitro, Animal and Epidemiological Evidence

Heleen K. Bronsveld,[1,6] Bas ter Braak,[2] Øystein Karlstad,[3] Peter Vestergaard,[4] Jakob Starup-Linde,[4,5] Marloes T. Bazelier,[6] Marie L. de Bruin,[6] Anthonius de Boer,[6] Christine L. E. Siezen,[7] Bob van de Water,[8] Jan Willem van der Laan,[2,7,8] and Marjanka K. Schmidt.[1] [1]*Division of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [2]*Division of Toxicology, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands;* [3]*Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo, Norway;* [4]*Departments of Clinical Medicine and Endocrinology, Aalborg University, Aalborg, Denmark;* [5]*Department of Endocrinology and Internal Medicine (MEA), Aarhus University Hospital THG, Aarhus, Denmark;* [6]*Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands;* [7]*Medicines Evaluation Board (MEB), Utrecht, The Netherlands;* [8]*Centre for Health Protection, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands.*

Background: In 2009, the concern has been raised that insulin analogues, especially insulin glargine, might increase risk of (breast) cancer. Many *in vitro* and epidemiological and some animal studies have been performed, but there is still no clarity on this issue.

Objectives: The aim of this study was to investigate the association between insulin and insulin analogue treatment and breast cancer development, and plausible mechanisms, based on *in vitro*, animal and epidemiological evidence.

Methods: A systematic literature search was performed on breast cell-line, animal and human studies

using the key words 'insulin analogue' and 'breast neoplasia' in MEDLINE at PubMed, EMBASE and ISI Web of Science databases. A quantitative and qualitative review was performed on the epidemiological data, and a complete overview was composed for *in vitro* and animal studies. Protein and gene expression was analysed for the cell lines most frequently used in the included *in vitro* studies.

Results: Sixteen *in vitro*, 5 animal, 2 *in vivo* human and 29 epidemiological papers were included. Insulin AspB10 showed mitogenic properties in *in vitro* and animal studies. Glargine was the only clinically available insulin analogue for which an increased proliferative potential was found in breast cancer cell lines. However, the pooled analysis of 13 epidemiological studies did not show evidence for an association between insulin glargine treatment and increased breast cancer risk (HR = 1.04, 95%CI = 0.91–1.17, $p = 0.49$) versus no glargine in patients with diabetes mellitus. It has to be taken into account that animal data were limited, and epidemiological studies were underpowered and suffered from methodological limitations.

Conclusions: There is no compelling evidence that any clinically available insulin analogue increases breast cancer risk. Overall, the data suggest that insulin treatment is not involved in breast tumour initiation but might induce breast tumour progression by up-regulating mitogenic signalling pathways.

88. Patient-Reported Health Utility Scores (HUS) in Non-small Cell Lung Cancer (NSCLC) Patients with Epidermal Growth Factor Receptor (EGFR) Mutations by Drug Therapy

Erin L. Stewart,[1] Catherine Labbe,[1] Catherine Brown,[1] Andrea Perez-Cosio,[1] Ashlee Vennettilli,[1] Devalben Patel,[1] Nicholas Cheng,[1] Mindy Liang,[1] Gursharan Gill,[1] Yvonne Leung,[1] Nicole Mittmann,[2] Hiten Naik,[1] and Geoffrey Liu.[1] [1]*Research, Princess Margaret Cancer Centre, Toronto, ON, Canada;* [2]*Odette Cancer Centre, Sunnybrook Hospital, Toronto, ON, Canada.*

Background: Health utility scores (HUS) help define quality-adjusted life years in pharmacoeconomic analyses. There are several approved epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in use worldwide for patients with non-small cell lung cancer (NSCLC), and many are still in development. A lack of reference HUS exists for these patients.

Objectives: The aim of this study was to generate patient-reported HUS in NSCLC patients with EGFR mutations eligible for or on TKI therapy.

Methods: Using a cross-sectional survey design, 55 consecutive metastatic NSCLC outpatients with EGFR mutations at Princess Margaret Cancer Centre completed clinico-epidemiologic surveys (risk factors, demographics, health status) and the EQ5D-3L questionnaire that generates HUS (0–1). Results were correlated with clinico-epidemiologic data.

Results: Median age was 60 years; 55% were female; 55% had Asian ancestry; 66% were never smokers; 80% had stage IV at diagnosis, but 100% had stage IV at the time of survey (at a median of 29 months after initial diagnosis). Eighty-four percent were on targeted therapy, 25% were on third or later line of therapy, and 22% were on a clinical trial. Sixty-two percent of patients were on first-generation EGFR TKIs (gefitinib, erlotinib), of whom 65% (95%CI: 46–80%) had partial response or stable disease (PR/SD). Twenty percent of patients were on third-generation EGFR TKIs (mostly AZ9291) of whom 80% (95%CI: 44–95%) had PR/SD. Overall mean ± SEM HUS = 0.802. The mean HUS for NSCLC patients with PR/SD on EGFR TKIs ($n = 31$) was 0.82 ± 0.16, while patients responding to standard chemotherapy had HUS = 0.80 ± 0.12 ($n = 5$). In contrast, patients with progressive disease during TKI therapy were associated with lower HUS = 0.74 ± 0.08. Patients that responded to gefitinib (HUS = 0.84 ± 0.14), to erlotinib (0.82 ± 0.17), or to AZD9291 (0.83 ± 0.16) had similar mean HUS values. Race, gender, time since diagnosis, smoking status and number of lines of therapy were each unassociated with HUS.

Conclusions: Response to TKI therapy may be an important driver of HUS, which were generally high. Mean HUS scores were similar across all major clinico-epidemiological factors; no HUS differences were found by specific TKI agent.

89. Frequency and Trends of Disease-Modifying Antirheumatic Drug (DMARD) Use in Germany

Alexander M. Fassmer, Edeltraut Garbe, and Niklas Schmedt. *Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH), Bremen, Germany.*

Background: The use of disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis

(RA) and various other indications has continuously increased in recent years. Population-based data on DMARD utilization is lacking for Germany.

Objectives: The aim of this study was to investigate the frequency, trends and underlying indications of DMARD use.

Methods: Based on claims data of the German Pharmacoepidemiological Research Database (GePaRD), yearly cross-sectional studies were conducted from 2004 to 2011. Insurants were included in the respective study population, if they were continuously insured during the study year or beginning with birth or until death. All outpatient dispensations of approved classical DMARDs (c-DMARDs) and biological DMARDs (b-DMARDs) in the respective study year were considered. For each study year, the prevalence of DMARD use was calculated as the number of persons with at least one DMARD dispensation per 1000 persons stratified by sex and age group. In 2011, we also obtained the proportion of c- and b-DMARDs users with a diagnosis for possible indications.

Results: The study population in 2011 comprised 12 774 731 persons of whom 55% were female. The mean age was 43.9 (SD 22.6 years). Between 2004 and 2011, the annual prevalence of b-DMARDs and c-DMARDs use increased from 0.35‰ to 1.54‰ and from 6.53‰ to 8.93‰, respectively (both: p for trend < 0.0001). In 2011, women more often received b- and c-DMARDs than men (1.7‰ vs. 1.3‰ and 11.1‰ vs. 3.3‰, respectively). The highest prevalence of c-DMARD use in 2011 was observed in the age group 70–79 (17.4‰), whereas b-DMARD use was most frequent in the age group 60–69 (2.42‰). Almost 50% of both c- and b-DMARD users had a diagnosis of RA. Compared with c-DMARDs, b-DMARDs users more often had a diagnosis of psoriasis and Bechterew's disease (11.8% vs. 18.3% and 3.3% vs. 14.3%, respectively).

Conclusions: Our population-based study highlights the increasing use of c- and b-DMARDs in Germany. Indications besides RA differed substantially for c- and b-DMARDs.

90. Clotting Factor Utilization Among the U.S. Elderly as Recorded in Medicare Databases During 2008–2013

Mikhail Menis,[1] Steven A. Anderson,[1] Stephen McKean,[2] Rob Warnock,[2] Mikhail V. Ovanesov,[1] Paul D. Mintz,[1] Sumit Verma,[2] Natalie Norton,[2] Zebulin Kessler,[2] Hector S. Izurieta,[1] Christopher M. Worrall,[3] Jeffrey A. Kelman,[3] and Richard A. Forshee.[1] *[1]FDA/CBER, Silver Spring, MD, USA; [2]Acumen LLC, Burlingame, CA, USA; [3]CMS, Baltimore, MD, USA.*

Background: Clotting factor (CF) products are biologics derived from plasma or recombinant technology. Although CFs are mostly approved for treatment of congenital factor deficiencies (CFDs), they are increasingly used off label.

Objectives: The aims of this study were to assess utilization of CFs and estimate potential off-label CF use among elderly Medicare beneficiaries, ages 65 and older.

Methods: This is a 6-year retrospective claims-based study of CF utilization among elderly Medicare beneficiaries from 1 January 2008 through 31 December 2013, using large Medicare databases. CF administrations were assessed by recorded procedure codes, and CFDs were ascertained using diagnosis codes. Study evaluated the number of elderly CF users and CF utilization rates (per 100 000 elderly Medicare beneficiaries), overall and by year, age, sex, race, service settings, states, and CFD status.

Results: Of 38 077 466 elderly Medicare beneficiaries in 2008–2013, 22 633 were CF product users, an overall cumulative rate of 59.4 CF users per 100 000. Annual CF use rates were 10.3, 11.4, 13.5, 16.9, 19.4, and 21.7, respectively. The majority of elderly CF users were ages 65–79 (66.4%), male (56.3%), White (86.4%), in the inpatient setting (76.7%), and did not have CFDs recorded (85.7%). CF use rates (per 100 000) for ages 65–79 and 80 and older were 52.2 and 57.1; for women and men, 46.0 and 76.8; and for Whites and non-Whites, 60.0 and 56.1. States with the highest CF use rates in elderly were Texas (116.2), West Virginia (102.0), North Dakota (101.2), Minnesota (94.3), and California (84.4). CFs rFVIIa, FIX complex, and rFVIII were the most frequently utilized products, representing 22.8%, 11.2%, and 9.8% of elderly CF users, respectively.

Conclusions: The study shows that CF product use among the elderly varies by year, age, gender, race, service setting, and states. The results suggest a potentially substantial off-label CF use in the elderly and show a possible trend of increasing CF utilization over time. Overall, our study shows usefulness of large administrative databases in identifying CF product

utilization patterns and will further help in assessment of CF safety in the elderly.

91. Comparison of Patients Initiating Abatacept and TNFs Enrolled in MarketScan and the ARTIS Registry

Nicole Baker,[1] Thomas Frisell,[2] Johan Askling,[2] Hugh Kawabata,[3] and Teresa A. Simon.[1] *[1]Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb Company, Hopewell, NJ, USA; [2]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Solna, Stockholm, Sweden; [3]Center for Observational Research and Data Sciences, Bristol-Myers Squibb Company, Hopewell, NJ, USA*

Background: Abatacept is the first selective costimulation modulator biologic approved for the treatment of rheumatoid arthritis (RA); it has a mechanism of action that is different from that of the tumor necrosis factor (TNF)-blocking agents. Patients initiating abatacept may differ from patients initiating TNFs. Describing baseline characteristics will provide a better understanding of these patients.

Objectives: The aim of this study was to compare baseline characteristics of patients with RA initiating abatacept and those initiating TNFs using data from a United States administrative claims database and a Swedish disease registry.

Methods: A retrospective cohort study was conducted to evaluate characteristics of patients with RA enrolled in MarketScan Commercial and Medicare Supplemental databases (MarketScan) who initiated abatacept or TNFs between July 2006 and June 2012. Comorbidities and comedications reported in the 180 days prior to initiation were captured. In addition, prospective data on patients initiating abatacept or TNFs as part of the Anti-Rheumatic Therapy in Sweden (ARTIS) Registry were collected between January 2006 and December 2012. Comorbidities recorded since 1968 and comedications used at initiation were captured. Patient characteristics, comorbidities and comedications were compared between the two data sources.

Results: Patients initiating abatacept were older and more likely to be female than patients initiating a TNF in MarketScan and ARTIS. Patterns of comorbidities and comedications between abatacept and TNF inhibitors were similar in the two data sources, but the percentages of patients with each comorbidity and comedication differed.

Conclusions: Additional work is needed to understand if differences between MarketScan and ARTIS are the result of the way in which the data were captured or if there are true differences between the populations enrolled.

92. Dyslipidaemia in HIV-Positive Patients Treated with Protease Inhibitors in the Cape Metropole Region: Preliminary Results

Pierre Mugabo,[1] and Richard Madsen.[2] *[1]School of Pharmacy, University of the Western Cape, Bellville/Cape Town, Western Cape, South Africa; [2]Department of Statistics, University of Missouri, Columbia, MO, USA.*

Background: Stavudine and non-nucleotide reverse transcriptase inhibitors can cause dyslipidaemia but to a lesser extent than protease inhibitors (PIs) (Yone, et al, 2012). The Western Cape Department of Health recommends therapeutic monitoring laboratory tests (TMLT) of serum total cholesterol (STC), serum triglycerides (STG), CD4 counts and viral load (VL) at baseline, 3 months and every year after starting PIs.

Objectives: The objectives of this study were (i) to find out whether PIs cause hypercholesterolaemia and hypertriglyceridaemia; (ii) to determine the influence of HIV infection, gender and age on STC and STG; and (iii) to investigate the level of adherence to therapeutic monitoring laboratory tests.

Methods: This study compares STC and STG at baseline, 3 months and every year after initiating PIs. It also assesses the compliance with TMLT by health workers. It involves HIV-infected patients, 0 to 65 years old, who received PIs between 2008 and 2012. The patient age and gender, STC, STG, CD4 counts and VL were recorded from patient folder and from the National Health Laboratory Services (NHLS) data base.

Results: Out of 753 patients (457 women and 296 men), 163 patients were 0 to 17 years old, 527 were 18 to 44 years old, 63 were above 45 years of age and 310 (41.14%) had consistent results during the study period. For STC, there was a significant overall time increase ($p = 0.0137$) with a significant difference from baseline at 3 years. For STG, the overall time

increase was not significant ($p = 0.4132$). There was a significant increase in CD4 and a significant decrease in VL from baseline to 3 months, and 1, 2 and 3 years. Gender and age did not show any significant relationship with STC and STG serum levels. Compliance with TMLT was 15–25% for STC and STG, 20–40% for VL, and 30–50% for CD4 counts.

Conclusions: This study results demonstrate hypercholestrolaemia in HIV-infected patients receiving PIs. There is no change in STG. Age and gender did not have any influence on STC and STG. Compliance with TMLT guidelines is poor.

93. Changes in Glucose Lowering Drug Use Before and After a Cancer Diagnosis Among Individuals with Diabetes

Marjolein Zanders,[1] Harm Haak,[2,3] Myrthe van Herk-Sukel,[4] Ron Herings,[4] Lonneke van de Poll-Franse,[1,5] and Jeffrey Johnson.[6] *[1]Netherlands Comprehensive Cancer Organisation, Eindhoven, The Netherlands; [2]Máxima Medical Centre, Veldhoven, The Netherlands; [3]Maastricht University Medical Centre, Maastricht, The Netherlands; [4]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [5]CoRPS—Center of Research on Psychology in Somatic Diseases, Tilburg, The Netherlands; [6]School of Public Health, University of Alberta, Edmonton, Canada.*

Background: Numerous epidemiological studies have shown that most cancers occur more commonly in individuals with type 2 diabetes than in the general population. Individuals with diabetes that use insulin-based therapies seemed to have even higher risks of developing certain cancers.

Objectives: The aim of this study was to better understand the association between glucose-lowering drug (GLDs), cancer risk and outcomes, and this study explores the changes in GLD use associated with cancer development and treatment among individuals with diabetes and subsequent cancer, taking into account the changes in GLD use among those without cancer.

Methods: New GLDs users (1998–2011) living in the Eindhoven Cancer Registry-PHARMO catchment area were selected ($n = 52\,228$). Those with a primary cancer diagnosis were considered cases ($n = 3{,}281$) and matched with eligible controls without cancer during follow-up ($n = 12\,891$). Conditional logistic regression analysis was used to assess changes in GLD use, that is, treatment drop and initiating insulin, for cases compared with controls owing to specific cancer types in four time windows (3–6 and 0–3 months before cancer diagnosis; 0–3 and 3–6 months after cancer diagnosis).

Results: In the 3–6 months before cancer diagnosis, gastrointestinal and pancreas cancers were associated with higher odds of starting with insulin (OR 3.9; 95%CI 1.3–12.1 and OR 4.9; 95%CI 1.3–18.1). Colorectal (OR 3.4; 95%CI 1.4–8.4) and gastrointestinal (OR 13.6; 95%CI 5.0–36.9) cancers were associated with increased odds of initiating insulin in the 3 months after cancer diagnosis. After this period, these odds were increased for breast (OR 4.6; 95%CI 1.7–12.6) and pulmonary (OR 3.3; 95%CI 1.2–9.1) cancers. Within all time windows, odds of treatment drops were higher for patients with gastrointestinal cancers, while for all other cancers (except breast and prostate), odds were only higher after cancer diagnosis.

Conclusions: Already 3 to 6 months before the diagnosis of gastrointestinal or pancreas cancer, higher odds of initiating insulin use were observed, suggesting reverse causation. Stopping GLDs was common after cancer diagnosis, while the diagnosis of most cancer types was associated with the start of insulin.

94. Implementation of a Comprehensive Treatment Center on Hemophilia CITH with Follow-Up Results at the First Year

Fernando Guerrero,[1] Carlos Ramirez,[1] Juliana Jacome,[1] Victor Machado,[2] Diana Ramos,[1] and Fabian Beltran.[2] *[1]Vicepresidencia de Ciencia y Tecnologia Farmacoepidemiologia, Organizacion Sanitas Internacional, EPS Sanitas, Bogotá, Colombia; [2]Direccion Tecnica, Farmasanitas, Bogotá, Colombia.*

Background: Hemophilia is an illness with treatment costs that may range from $41 000 to $2m, a condition that has not allowed to establish an effectiveness cost threshold adequate for the healthcare systems. In Colombia, the development of care models in health care varies, but generally, it does not have management programs for blood products or biotechnological pharmacological products; it does not count with a unified registry of patients, despite having medics who are trained in the illness, and they are not integrated as a multi-disciplinary group.

Objectives: The aim of this study was to describe the results of the implementation of a CITH associated to a management model of medications.

Methods: Descriptive analysis of a cohort of hemophiliac populations and other blood dyscrasias in five cities in Colombia.

Results: A total of 110 patients were included, with hemophilia 58% (A, 67%; B, 21%; C, 3; carrier, 9%), VW 30%, and other dyscrasias 12%. Bogotá 86%, other regions 14%. Prevalence 0.48 and 1, hemophilia A, 0.78; B, 0.24; C, 0.04 (×10 000). Slight hemophilia 24%, moderate 24% and severe 49%, distributed within the groups of 0–4 years 9%, 5–19 years 23%, 20–44 years 47% and >45 years of age 21%. In Bogotá, under the prophylaxis scheme 51% (A, 90%; B, 10%). Rate of inhibitors of 4.5%. Bleeding events 1–19 in 12 months, without deficiencies in proportions owing to the type of factor used (recombinant/plasma). Presence of hemophiliac arthropathy 51%, hepatitis 33%. The rate per capita of factor VIII was 1.7 and 3.9 UI, with a proportion of 1/1 of recombinant versus plasma factor. In the regions other than Bogotá, all the patients had the prophylaxis scheme, and two cases had inhibitors with a high title, which were found with IIT.

Conclusions: The structuring of our CITH allowed for the optimization of the access and adequate use of the blood derived or biotechnological medications and binding them to the clinical follow-up. The per capita rate of the use found is located within the report for countries of that region. The most frequent condition associated to the appearance of bleeding may be related to the modifications of schedules of administration, changes in days of schemes and self-infusion at home.

95. Impact of a Decree on ACE Inhibitors/ARBs in Cardiovascular Secondary Prevention in the Lazio Region: A Pre–Post Analysis

Flavia Mayer, Ursula Kirchmayer, Mirko Di Martino, Nera Agabiti, Danilo Fusco, and Maria Davoli. *Department of Epidemiology, Lazio Regional Health Service, Rome, Italy.*

Background: In 2010, the Lazio region introduced a legal decree on prescribing of agents acting on the renin–angiotensin system.

Objectives: The aim of this study was to evaluate the effect of the Commission Decree Ad Acta (dCa) in 2010, which promotes the appropriateness of drug use for patients with cardiovascular disease (CVD), aiming at an increase of the overall prescriptions of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) with a reduction in proportion of ARBs prescriptions below 30%.

Methods: From the regional hospital admission registry, two cohorts of incidents patients with diagnosis of CVD were enrolled: the first one in the 12 months before dCa and the second one in the 12 months after dCa. Drug claims registry was used to link prescription of ACE/ARBs in the 30 days after index discharge to every patients, distinguishing between hospital and specialist physician prescription in the Lazio region. Through a segmented regression analysis, trends of monthly prescription proportion for the two different drugs were compared between the pre-dCa period and post-dCa period.

Results: Proportion of patients with CVD treated with ACE/ARBs in the 30 days after discharge was 50% in both pre-dCa (35 917 patients) and post-dCa (35 491 patients) cohorts with the same share of ACE (60%) and ARBs (40%).

ARBs prescription proportion decrease below the threshold of 30% during post-dCa period only for hospital prescriptions. Instead, for the sub-population of new users for ACE/ARBs, the threshold of 30% is reached for both hospital and specialist physician prescription.

Conclusions: The specific dCa has not led to an overall improvement in the appropriateness of prescribing ACE/ARBs in cardiovascular secondary prevention. However, there is a suitable prescription choice for naïve patients and when the drug is dispensed in hospitals.

96. Withdrawn by author

97. Impact of a Public Intervention in the Media on the Use of Statins in Patients at Various Cardiovascular Risks

Julien Bezin,[1] Florence Francis,[2] Nam Vinh Nguyen,[3] and Nicholas Moore.[1] *[1]Université de Bordeaux, INSERM U657, CHU de Bordeaux, CIC Bordeaux CIC1401, Bordeaux, France; [2]Université de Bordeaux, CHU de Bordeaux, Bordeaux, France; [3]Université de Bordeaux, Bordeaux, France.*

Background: In February 2013, a renowned professor published a book denying the utility of statins for

cardiovascular (CV) prevention, which was the object of much media coverage, and multiple public discussions and debate.

Objectives: The aim of this study was to evaluate the impact of this public discussion on the use of statins in populations at various CV risk levels.

Methods: We performed a repeated cohort study in the 1/97th permanent representative sample of the French national healthcare insurance database. Primary cohort included regular statin users during the 1-year period before 31 January 2013. Patients were followed up during 8 months after 1 February 2013. To provide baseline information on statin use trends in the French population, three reference cohorts corresponding to the previous 3 years (2010, 2011, and 2012) were constituted using the same design and the same definition of periods. Statin discontinuation was defined by a gap of more than 90 days between two treatment periods. Patients were classified into three CV risk statuses: high CV risk (coronary disease or ischemic stroke), moderate CV risk (diabetes or CV co-medications) and low CV risk (none of the previous factors).

Results: A total of 30 698 patients were included in the primary cohort: 27 945 in 2012, 28 249 in 2011 and 24 236 in 2010 reference cohorts. The probability of statin discontinuation at 8 months of follow-up was 8.1% (95%CI [7.8; 8.4]) in the primary cohort, 5.1% (95%CI [4.8; 5.3]) in 2012, 5.4% (95%CI [5.1; 5.6]) in 2011 and 4.5% (95%CI [4.3; 4.8]) in 2010 reference cohorts. The discontinuation rate was higher in the low CV risk group than in the other risk groups: 13.9% (95%CI [12.9; 15.0]) in the primary cohort, 7.5% (95%CI [6.7; 8.4]) in 2012, 7.2% (95%CI [6.4; 8.0]) in 2011 and 6.7% (95%CI [5.9; 7.6]) in 2010 reference cohorts.

Conclusions: Statin discontinuation among regular users was not very different after February 2013 than in the other reference years. However, in patients with low CV risk, statin discontinuation was about double in 2013 than in previous years, maybe because of the media intervention. The health impact of this discontinuation remains to be demonstrated.

98. The Impact of Direct-to-Consumer Advertising on Testosterone Testing and Initiation in the United States

J. Bradley Layton,[1] Yoonsang Kim,[2] Glen Szcypka,[2] G. Caleb Alexander,[3] M. Alan Brookhart,[1] Matthew Daubresse,[3] and Sherry L. Emery.[2] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Institute for Health Research & Policy, University of Illinois at Chicago, Chicago, IL, USA; [3]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA.*

Background: Testosterone testing and prescription testosterone use have increased substantially over the previous decade amid continuing disagreement about necessity and safety of widespread treatment among middle-aged and older men. These increases have been largest in the USA, which permits direct-to-consumer advertising (DTCA) of prescription pharmaceuticals.

Objectives: The aim of this study was to estimate the impact of DTCA on new testosterone testing and initiation in the USA.

Methods: Monthly Nielsen ratings were collected for television advertisements for branded, prescription testosterone and non-branded, condition-awareness ads for the 75 largest designated market areas (DMA) in the USA, years 2009–2012. Ratings were standardized so that a one-unit increase in ratings represented an average of one additional viewing of a television ad per household in a given month. The number of men initiating testosterone and newly testing for testosterone blood levels was estimated for each DMA from commercial insurance claims databases and linked to the previous month's advertising data. DMA demographic characteristics were collected from census information. The impact of marketing on testosterone use in the next month was estimated using Poison generalized estimating equations, adjusted for usage time trends and demographics.

Results: We observed large variations in advertising intensity over time, with months ranging from no ads to approximately nine ad views per household per month in a DMA. Non-branded advertisements were common earlier in the time period, with branded, product-specific advertisements becoming more common later. After adjusting for DMA-level characteristics, a monthly increase of 0.6% (95%CI: 0.2–0.9%) in new testosterone testing rate and 0.6% (95%CI: 0.2–1.1%) in new initiation rate were associated with each additional advertisement viewing per household. There was wide geographic variation in advertising intensity, with the highest concentration seen in the southeastern USA.

Conclusions: Direct-to-consumer promotion of testosterone products and condition-awareness ads increased

testosterone testing and initiation among adult men in the USA.

99. Patient Characteristics and Prior Total Knee Arthroplasty Opioid Use Are Associated with Post-operative Opioid Use

Maria C. S. Inacio,[1,2] Robert S. Namba,[3] Anshuman Singh,[4] Cheetham T. Craig,[5] and Elizabeth W. Paxton.[2] *[1]Surgical Outcomes and Analysis, Kaiser Permanente, San Diego, CA, USA; [2]School of Pharmacy, University of South Australia, Adelaide, South Australia, Australia; [3]Orthopaedics, Southern California Permanente Medical Group, Kaiser Permanente, Irvine, CA, USA; [4]Orthopaedics, Southern California Permanente Medical Group, Kaiser Permanente, San Diego, CA, USA; [5]Research & Evaluation, Southern California Permanente Medical Group, Kaiser Permanente, Pasadena, CA, USA.*

Background: Pain is a main surgical indication for total knee arthroplasty (TKA). Although pain relief is expected after surgery, pain persists in one-third of patients. Identifying patients at higher risk for persistent pain can improve patient care.

Objectives: The aim of this study was to identify pre-operative factors associated with increased amounts of opioid prescriptions following TKA surgery.

Methods: A cohort study of TKAs performed in an integrated healthcare system (January 2008 to December 2011) was conducted. The number of opioid prescriptions per 90 day period after TKA (up to a full year) was the outcome of interest. The pre-operative risk factors evaluated were demographics, pain prescription use, patient co-morbidities, and other types of chronic pain. Poisson regression models were employed, and odds ratios (OR) and 95% confidence intervals (CIs) are presented.

Results: Of the 23 726 patients studied, 62.9% ($N = 14\,907$) were women, 65.9% (15 638) were White, and the median age was 67 years old. In the year prior to TKA, 60.0% ($N = 14\,234$) used opioids (72 716 prescriptions dispensed). After the first 90 days (days ≥ 91 to 360) following surgery, at least 41.2% ($N = 9993$) of patients continued using opioids ($N = 55\,873$ prescriptions dispensed). The stronger risk factors associated with having a greater number of opioid prescriptions during post-operative days 91–180 were pre-operative opioid prescriptions (OR = 1.1, 95%CI 1.1–1.1), female gender (OR = 1.1, 95%CI 1.0–1.1), Black (OR = 1.2, 95%CI 1.1–1.2) and Hispanic individuals (OR = 1.1, 95% 1.1–1.2), anxiety (OR = 1.1, 95%CI 1.1–1.2), depression (OR = 1.1, 95%CI 1.1–1.2), substance abuse (OR = 1.2, 95%CI 1.2–1.3), congestive heart failure (OR = 1.2, 95%CI 1.1–1.3), liver disease (OR = 1.2, 95%CI 1.1–1.4), back pain (OR = 1.2, 95% CI 1.2–1.3), and costochondritis/intracostal muscle injury (OR = 1.5, 95%CI 1.1–2.0). Most risk factors were consistent for prescriptions dispensed days 181–270 and 271–360 after surgery.

Conclusions: Several pre-operative factors were associated with increased post-operative opioid prescriptions. Identification of these factors can assist orthopedic surgeons in managing patients' expectations and guide management of their postoperative course.

100. Acetaminophen Overdosing in Hospitalized Patients: Retrospective Analysis and Implementation of Preventive Semi-automated Alerts

David F. Niedrig,[1,2] Guido Bucklar,[3] Michael Fetzer,[3] Sarah Maechler,[1] Carmen Goett,[1] Gerd A. Kullak-Ublick,[1] and Stefan Russmann.[1,2] *[1]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland; [2]Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland; [3]Research Centre Medical Informatics, University Hospital Zurich, Zurich, Switzerland.*

Background: Acetaminophen is a widely used analgesic, a dose-dependent hepatotoxin, and the most frequent cause of acute liver failure in Western countries. A study from the USA reported that supratherapeutic dosing with >4 g/day occurred in 6.6% of hospitalized patients receiving acetaminophen.

Objectives: We aimed to analyze supratherapeutic acetaminophen dosing in a Swiss hospital setting and to implement an alert system for the prevention of repeated overdosing.

Methods: For the retrospective analysis of overdosing, we set up a pharmacoepidemiological database based on a hospital's clinical information system and analyzed all documented acetaminophen administrations from 2011 to 2013. In 2014, we installed an alert system with proactive monitoring of total acetaminophen doses per day in hospitalized patients. In order to focus on clinical

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relevance and to prevent alert fatigue, subsequent warnings to physicians were only issued if the current acetaminophen prescription permitted repeated dosing of ≥5 g day or as soon as patients had once received ≥6 g day.

Results: In the retrospective analysis covering three calendar years, a total of 49 357 patients had been administered acetaminophen during hospitalization. Among those, we found that 2965 patients (6.0%) had received >4 g day and 119 (0.24%) ≥6 g day. In 11 patients, we identified repeated overdosing with 5 to 8 g day for more than two consecutive days. In 2014, our newly implemented automated timely alert algorithm identified 33 patients at risk of clinically relevant overdosing where we issued an alert to the prescribing physician. Subsequently, acetaminophen administrations of ≥5 g day for more than two consecutive days did not occur anymore in 2014, suggesting 100% efficacy of our alerts regarding the prevention of clinically relevant overdosing.

Conclusions: Repeated acetaminophen overdosing is a ubiquitous and frequent medication error. Our alert system used a rational threshold for clinical relevance and prevented overdosing with high efficacy and efficiency but without causing alert fatigue.

101. Changes in US Oral Anticoagulant Drug Prescription Patterns During Period of FDA Actions

Cathy Anne Pinto,[1] Yong Chen,[2] Jianmin Wu,[3] and Tarek Hammad.[2] *[1]Pharmacoepidemiology, Merck Research Laboratories, Rahway, NJ, USA; [2]Pharmacoepidemioloy, Merck Research Laboratories, Upper Gwynedd, PA, USA; [3]Biomedical Informatics, Regenstrief Institute, Inc., Indianapolis, IN, USA.*

Background: Following US approval, the FDA received a large number of postmarketing reports of bleeding among dabigatran users, which prompted a 2011 safety alert stating plans to further assess bleeding rates and a 2012 alert with results of a Mini-Sentinel modular assessment, which showed no increase in rates associated with new dabigatran use. The FDA also announced plans in 2013 for a detailed protocol assessment using the Sentinel system, which is currently underway. However, it is unclear what impact, if any, the initial safety alerts had on dabigatran utilization patterns.

Objectives: The aim of the study was to evaluate changes in new dabigatran use in a US cohort of non-valvular atrial fibrillation (NVAF) patients surrounding the 2011 and 2012 FDA safety alerts.

Methods: NVAF patients ≥21 years of age identified in the Humana claims database between November 2010 and 2013 were included in a rolling monthly cohort. Incident use for dabigatran, a more commonly used anticoagulant (warfarin), and a negative control (H2 agonist) with no anticipated change was defined as the #new users/#cohort members 'at risk' of medication use. New users and 'at risk' cohort members had no evidence of drug use within 365 days of each month. A segmented regression model was used to analyze the time series data and estimate patterns (level, trend) of utilization after each alert, adjusting for use before the intervention. Assuming the impact was not immediately visible, a 1-month transition gap after the alert was used to define the time series. Sensitivity analyses used no gap and a 1-month gap prior to each alert.

Results: A significant change in the slope of dabigatran use was consistently observed coincident with the 2011 ($p \leq 0.001$) and 2012 ($p < 0.05$) alerts, with a significant change in the level of use surrounding the first safety alert. Significant changes in the slope of warfarin use inversely tracked with changes in dabigatran use.

Conclusions: A change in the trend of new dabigatran use coincided with the 2011 and 2012 FDA safety alerts.

102. Impacts of Established Academic Detailing Programs on Prescribing Across Canada

David Blackburn,[1] Nancy Blythe,[2] Michael Allen,[3] Anne Nguyen,[2] Tanya MacLeod,[3] Loren Regier,[4] Michelle Boudreau,[3] Tom Briggs,[5] and Malcolm Maclure.[2] *[1]University of Saskatchewan, Saskatoon, SK, Canada; [2]University of British Columbia, Vancouver, BC, Canada; [3]Dalhousie University, Halifax, NS, Canada; [4]RxFiles—Academic Detailing Program, Saskatoon, SK, Canada; [5]Alberta Health Services, Edmonton, AB, Canada.*

Background: Systematic reviews indicate academic detailing (AD)—educational outreach visits to family physicians (FPs)—can influence prescribing, but solid evidence is needed of real-world impacts of established programs. AD programs in four Canadian provinces collaborated on evaluating impacts of five educational modules delivered between 2008 and 2013.

Objectives: The aim of this study was to measure short-term impacts of real-world AD on prescribing and identify factors that might modify their effect.

Methods: Participating FPs ($n > 1000$) were assigned, with randomization in British Columbia (BC), Nova Scotia (NS) and Alberta (AB) and without randomization in Saskatchewan (SK), to early or delayed AD visits. Using drug claims databases and controlled before–after and times-series designs, differences in prescribing preferences (conditional probabilities) for target drugs were compared between participants and nonparticipants, and between early and delayed groups, adjusting for baseline differences. The mean adjusted preference difference (APD) was estimated by meta-analysis across drugs and provinces (after multiplying any difference by −1 if AD discouraged prescribing of such a drug.)

Results: Comparing participants versus nonparticipants, APDs for antibiotics in BC and NS ranged from −6% to 18% with mean = 6.5% (95% confidence interval [CI] from 5.9% to 7.1%); APDs for bisphosphonates in SK and NS ranged from −6% to 10% with mean = 2.4% (CI: 1.7% to 3.2%). Comparing early versus delayed, the mean APD for antibiotics was 7.2% (CI: 5.6% to 8.7%) and, for bisphosphonates in SK, 5.3% (CI: −0.6% to 11.2%). No measureable impacts of AD were observed for chronic non-cancer pain (i.e., opioid use) or heart failure (i.e., neurohormonal medication use) in SK, where control physicians might have accessed printed materials. No impact of AD on type 2 diabetes (i.e., insulin and metformin use) was seen in AB where the sample was small.

Conclusions: Routine AD on antibiotics had impacts similar to results of published meta-analyses of AD studies, many of which were research projects. With more complex topics and multiple messages, AD impacts were harder to measure and showed no consistent effect.

103. Effect of Prescription Drug Coupons on Statin Utilization and Expenditures: A Retrospective Cohort Study

Matthew Daubresse,[1] Martin Andersen,[2] Kevin R. Riggs,[1] and G. Caleb Alexander.[1] [1]*Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA;* [2]*Department of Economics, University of North Carolina at Greensboro, Greensboro, NC, USA.*

Background: Drug coupons are commonly used, yet their effect remains unclear.

Objectives: The aim of this study was to quantify the effect of coupons on statin use and expenditures.

Methods: We performed a retrospective cohort analysis among incident statin patients using longitudinal retail pharmacy claims from IMS Health Lifelink database. We compared statin patients with any coupon use to non-coupon users from July 2006 through August 2013, stratifying on whether the coupon was for a statin or another prescription drug. We used generalized estimating equations models, accounting for within-subject correlations over time, to quantify the effects of coupons on costs (out-of-pocket and total), adherence (pill counts and terminating statin therapy), and switching (probability of switching statin from 1 month to the next) following an index statin fill. We controlled for differences in patient age, gender, time on drug, and comorbidities. In sensitivity analyses, we varied requirements for continuous patient observation, patient stockpiling, and coupon use on first rather than subsequent statin fills.

Results: Of 1.8 million incident statin users observed between 2006 and 2013, 1.2% used a coupon for at least one statin fill. Based on preliminary results, the average monthly out-of-pocket and total pharmacy costs for patient who used a statin coupon on their first fill was $8 and $39 higher than those of non-coupon users at 1 month, respectively. After 12 months, the difference in monthly copay increased to $11 and persisted through year 4, whereas differences in total pharmacy costs declined substantially, although remaining $6 to $10 higher per month for coupon users than non-users. There were no appreciable differences in adherence between statin coupon users and non-users at various follow-up intervals beyond 1 month. The probability of switching was higher for statin coupon users (21%, 95% confidence interval [CI] 18.8–22.6%) compared with non-users after 12 months (15%, CI 14.7–15.4%). Sensitivity analyses supported the main results.

Conclusions: Among this cohort, coupons for statins were associated with higher costs and rates of switching, yet no difference in statin adherence.

104. An Intervention to Optimise Medication Use in Nursing Home Residents with Advanced Dementia: OptimaMed

Edeltraut Kroeger,[1,2] Machelle Wilchesky,[3,4] Philippe Voyer,[1,2] Michèle Morin,[1,2] Nathalie Champoux,[5]

Johanne Monette,[3] Anik Giguère,[1,2] Michèle Aubin,[1,2] Pierre Durand,[1,2] Marcel Arcand,[6] and René Verreault.[1,2] *[1]Université Laval, Québec, QC, Canada; [2]Centre d'Excellence sur le Vieillissement de Québec, Québec, QC, Canada; [3]McGill University, Montreal, QC, Canada; [4]Donald Berman Maimonides Geriatric Centre, Montreal, QC, Canada; [5]Université de Montréal, Montreal, QC, Canada; [6]Université de Sherbrooke, Sherbrooke, QC, Canada.*

Background: Nursing home (NH) residents with advanced dementia often receive multiple medications. With disease progression, care goals shift from curative or preventive care to comfort care, and medications must be reviewed, adjusted or discontinued because of reduced life expectancy or changes in the harm–benefit ratio. Few studies assessed interventions to achieve this goal.

Objectives: The aim of this study was to evaluate the feasibility of an inter-professional intervention to optimise medication use for NH residents with advanced dementia.

Methods: A literature review and multidisciplinary Delphi panel identified mostly, sometimes or rarely appropriate medications and elements of successful interventions. Medication lists and training sessions were tailored for a NH pilot study. A 4 months' intervention was led in three NH in Quebec, Canada. The families of participating residents received information on optimal medication use in advanced dementia and were invited to consent to the study. NH nurses, pharmacists and physicians participated in two 90-minute training sessions. For each participant, the pharmacist reviewed medications using the lists and discussed recommendations with nurses and physicians. A study nurse observed the comfort and agitation levels of participants using the Cohen–Mansfield and the PACSLAC-F scales during the study period.

Results: A total of 93 residents were eligible, and 45 could be observed over 4 months. A total of 38 health professionals participated in the training sessions. Medication lists were well accepted, and the study nurse was present at the discussions about medication changes. Families' and staffs' comments will allow improving information material and the tailored lists. Some changes in medications were observed; levels of agitation and comfort did not change noticeably. An interdisciplinary NH intervention to optimise medication use in residents with advanced dementia is feasible. The NH was interested in tools facilitating improved medication use.

Conclusions: A future cluster randomized trial may assess patient and family outcomes and the generalizability of the intervention; information for families should be a study focus.

105. Impact of Academic Detailing Program to Primary Care Providers About Antipsychotic Medication

Eimir Hurley,[1,2] Connie DiCocco,[2] Michael Fischer,[1,2] Niteesh Choudhry,[1,2] and Jerry Avorn.[1,2] *[1]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA, USA; [2]Alosa Foundation, Boston, MA, USA.*

Background: Antipsychotic medications (APMs) are widely used to control behavioral symptoms in elderly patients with dementia, despite lack of evidence of benefit and substantial risk of harm. Academic detailing (AD) is a program of proactive educational outreach of evidence-based prescribing guidance shown to improve medication use. We implemented an AD program for primary care physicians in Pennsylvania, reviewing the risks of APMs in elderly patients, presenting efficacy data for conditions in which they are frequently used, and offering safer alternatives.

Objectives: The aim of this study was to evaluate the impact of the program on prescribing of APMs to elderly patients.

Methods: We identified prescribers who participated in the program between April 2012 and March 2013, were high baseline prescribers of APMs, and were actively prescribed any medications in the subsequent 12 months. For each provider, we used paid claims data from Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) to quantify the number of filled APM prescriptions and the number of patients receiving those prescriptions in the 12 months pre-intervention and post-intervention. Prescribing rates were calculated per 30-day interval. Each prescriber was weighted by their overall level of prescribing activity to account for a downward trend in all prescribing through PACE during this time.

Results: Of the 621 prescribers who received the intervention, 173 were higher APM prescribers (≥12 APM prescriptions in baseline 12 months). The mean rate

over 12 months of APM Rx/1000 Rx per prescriber fell from 15.2 to 13.7, a relative reduction of 10% ($p = 0.0235$; paired t-test). Similar reductions were seen in the number of patients prescribed an APM: from 43.3/1000 patients to 39.3/1000 patients, a relative reduction of 9% ($p = 0.0185$, paired t-test).

Conclusions: An AD program for primary care physicians to reduce the overuse of APMs in the community-dwelling elderly achieved reductions in APM prescribing by clinicians who wrote at least one APM prescription/month at baseline. The evaluation found a decline in both the volume of prescribing and the number of PACE beneficiaries filling prescriptions for an APM.

106. Induction Agent Use in Older Kidney Transplant Recipients

Mara A. McAdams-DeMarco,[1] Xun Luo,[2] and Dorry Segev.[1,2] *[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2]Department of Surgery, Johns Hopkins School of Medicine, Baltimore, MD, USA.*

Background: Induction agents are commonly used as an initial intensive immunosuppression after kidney transplantation (KT) to prevent acute organ rejection; this practice is mostly off label. Little is known about induction agent use in older KT recipients.

Objectives: The aim of this study was to study the utilization, determinants, and consequences of induction agents in older KT recipients.

Methods: Data on 19 546 older KT recipients (2005–2013) were ascertained from the Scientific Registry of Transplant Recipients, a national registry of all solid organ transplants; each transplant center uniformly reports recipient, donor, and transplant factors. Induction agents were classified as thymoglobulin/antithymocyte globulin (ATG), IL-2, or other induction agents. The recipient factors (age, sex, race, body mass index, peak panel reactive antibody (PRA), history of diabetes, years on dialysis, and hepatitis C virus) and KT factors (human leukocyte antigen (HLA) mismatches, cold ischemia time, donor type, donor age, and donor sex) of older adults who received an induction agent (relative risk (RR)) was estimated using modified Poisson regression. The risk of mortality was estimated using a Cox proportional hazards model (hazard ratio (HR)) adjusting for all recipient and KT factors.

Results: The mean age was 69 (SD = 3.8 years), with 36% female, 19% Black, and 27% live donor recipients. There is an increasing utilization by year of induction agents, with 84% use in older recipients. The only recipient and KT factors associated with induction use in older recipients were Black recipients (RR = 0.96, 95%CI: 0.95–0.98, $p < 0.001$), peak PRA > 80 (RR = 1.05, 95%CI: 1.02–1.07, $p < 0.001$), 0 HLA mismatches (RR = 0.97, 95%CI: 0.95–0.99, $p = 0.04$), donation after cardiac death (RR = 1.05, 95%CI: 1.03–1.07, $p < 0.001$) and expanded criteria donation (RR = 1.02, 95%CI: 1.03–1.07, $p = 0.01$). Compared with those who did not receive induction, the risk of mortality for older recipients was decreased for those who received thymoglobulin/ATG (HR = 0.86, 95%CI: 0.79–0.94), IL-2 induction agents (HR = 0.89, 95%CI: 0.81–0.97), and other induction agents (HR = 0.85, 95%CI: 0.75–0.97).

Conclusions: For older KT recipients, there is an increasing trend in the use of induction agents. Older recipients who received an induction agent had a decreased risk of mortality regardless of the type of agent used.

107. Antibiotic Utilization Trends in the Veterans Affairs (VA) New England Healthcare System

Ajinkya M. Pawar,[1] Haley J. Morrill,[1,2] Kerry L. LaPlante,[1,2] and Aisling R. Caffrey.[1,2] *[1]College of Pharmacy, University of Rhode Island, Kingston, RI, USA; [2]Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA.*

Background: Antimicrobial resistance (AMR) is a global public health concern, which continues to increase. One of the major driving forces that selects for antimicrobial-resistant bacteria is antimicrobial use (known as antimicrobial pressure).

Objectives: The aim of this study was to quantify changes in antimicrobial utilization among five Veterans Affairs (VA) hospitals in New England.

Methods: Using inpatient and outpatient antibiotic dispensing data, we calculated days of therapy (DOT) per 1000 patient-days (PD) from 2005 to 2011. Modeled yearly changes in DOTs/1000 PD were assessed using generalized linear mixed model with gaussian distribution and identity link.

Results: The total antibiotic use was 3 303 709 DOT (11 191.4 DOT/1000 PD, inpatient = 14.8%,

outpatient = 85.2%) with an average of 20 520 DOT per year. Trimethoprim/sulfamethoxazole had the highest utilization of 905 179 DOT (3052.8 DOT/1000 PD, 27.4%), followed by 880 956.0 DOT (3004.1 DOT/1000 PD, 26.7%) for doxycycline and 564 707.5 DOT (1913.1 DOT/1000 PD, 17.1%) for ciprofloxacin. Average utilization per 1000 PD per year was 30.0 DOT for piperacillin/tazobactam, 18.3 for ceftriaxone, 5.3 for ampicillin, 4.6 for gentamicin, 1.0 for ertapenem, and 0.5 for amikacin. Based on the annualized modeled change in antibiotic utilization, ampicillin increased significantly each year by 1.3 DOT/1000 PD, as did ceftriaxone by 5.5 DOT/1000 PD, ertapenem by 0.3 DOT/1000 PD, and piperacillin/tazobactam by 8.8 DOT/1000 PD each year (all p-values < 0.05). Conversely, significant annual decreases in antibiotic use were observed for amikacin (0.2 DOT/1000 PD) and gentamicin (0.6 DOT/1000 PD).

Conclusions: Our study identified changing patterns in antibiotic utilization over the past 7 years in the VA New England regional healthcare system. These results are useful for informing antimicrobial stewardship programs, which assess antibiotic utilization and resistance patterns to guide treatment pathways, including empiric therapy, in order to improve antimicrobial use and decrease AMR. As such, further studies are needed to evaluate the impact of this changing antibiotic pressure on antimicrobial resistance.

108. Effectiveness of Interventions for Drug Prescribing Improvement in Primary Health Care

Marco A. Zavala-Gonzalez, Carlos E. Cabrera-Pivaral, Maria J. Orozco-Valerio. *University Center of Health Sciences, University of Guadalajara, Guadalajara, Jalisco, Mexico.*

Background: It has calculated that 50% to 90% drug prescribing are inappropriate worldwide. Various interventions to resolve this problem had been documented, informing variable effectiveness. Consensus over interventions effectiveness does not exist, and neither does the cost–benefit relationship.

Objectives: The aim of this study was to determine effectiveness of interventions for drug prescribing improvement in primary healthcare units.

Methods: We performed a systematic review and meta-analysis. We searched in MedLine©, Science Direct©, Springer©, SciELO©, Dialnet©, RedALyC©, and Imbiomed©, since indexation date of each database until August 2014. Keywords utilized were "drug prescribing", "intervention studies," and "primary health care" with corresponding synonyms. Quantitative studies included were experimental and quasi-experimental, written in Spanish, English or Portuguese, and published in any country, with Critical Appraisal Skills Programme score equal or major than five, where drug-prescribing quality was evaluated according to physicians' adherence to drug posology and Mexican guidelines for diseases treatment. Studies excluded were without raw data, qualitative studies, systematic reviews, protocols, essays, government documents, non-pharmacologic or alternative treatment studies and gray literature. Odds ratios (OR) with 95% interval confidence ($p = 0.05$) were obtained.

Results: We found 522 publications and excluded 405 for title, 99 for abstract and 9 for full text. We included three of the references. We did not find reference citations. We analyzed 12 articles that reported 17 interventions: 64.7% educative, 23.5% incorporating degrees in pharmacy to the health team and 11.8% software utilization. The association forces "intervention/improvement" obtained were as follows: educative interventions OR = 2.47 (95%CI 2.28, 2.69), incorporating degrees in pharmacy to the health team OR = 3.28 (95%CI 2.58, 4.18) and software utilization OR = 10.16 (95%CI 8.81, 11.71).

Conclusions: The software utilization interventions showed major effectiveness to improvement of drug-prescribing quality versus educative interventions and incorporation of degrees in pharmacy to the health team. However, educative interventions may have a better cost–benefit relationship.

109. Effects of Over-the-Counter Sales Restriction of Antibiotics on Substitution with Analgesics, Non-steroidal Anti-inflammatory Products and Cough and Cold Medication in Mexico and Brazil

Yared Santa-Ana-Tellez,[1] Aukje K. Mantel-Teeuwisse,[1] Hubert G.M. Leufkens,[1] and Veronika J. Wirtz.[2,3] *[1]WHO Collaborating Centre for Pharmaceutical Policy & Regulation, Utrecht Institute for Pharmaceutical Sciences (UIPS) Utrecht University, Utrecht, The Netherlands; [2]Center for Global Health and Development, Boston University, Boston, MA, USA; [3]Center for*

Health Systems Research, National Institute of Public Health, Cuernavaca, Morelos, Mexico.

Background: After the over-the-counter (OTC) antibiotic sales restrictions in Mexico and Brazil, consumers may have substituted antibiotics with other medicines such as analgesics, anti-inflammatory products, or preparations to diminish cough and cold symptoms.

Objectives: The aim of this study was to explore changes in the use of these medicines and its relation with the use of antibiotics.

Methods: IMS Health provided retail quarterly sales data from the private sectors in Mexico and Brazil from the first quarter of 2007 to the first quarter of 2013. Data of each active substance of antibiotics, easily accessible medicines perceived as antibiotics substitutes (cough and cold preparations (CCP), analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs)), and medicines to control external factors that can affect the trend of medicines use (antihypertensives) were converted from kilograms to defined daily doses per 1000 inhabitants days (DDD/TID). Interrupted time series models were used to estimate changes in slope and level of medicines use after the regulation. The Gregory–Hansen cointegration test was used to explore the relation between the antibiotics use and the easily accessible medicines use.

Results: After the regulation in Mexico, CCP use did not change, NSAID use had a 0.1 DDD/TID per quarter slope increase ($p < 0.001$), and analgesic use had a 0.7 DDD/TID level increase ($p < 0.001$). In Brazil, CCP use had a 0.05 DDD/TID per quarter slope decrease ($p = 0.057$) and 0.3 DDD/TID level decrease ($p = 0.059$), NSAID had a 0.2 DDD/TID per quarter slope increase ($p = 0.064$), and analgesics use did not change. In both countries, antibiotic use was not related with CCP use, but antibiotic use was related with NSAID use. Just in Mexico, antibiotic use was related with analgesic use.

Conclusions: These results showed that regulations to improve antibiotics use had a substitution effect on the use of other medicines, especially NSAIDs. The OTC antibiotic sales restrictions should be comprehensive and should take into account the potential substitution effects on other medicines usage.

110. Drug Safety Manager—Development of an Integrated Concept and Application for Drug Safety Analyses, Interventions and Outcomes Research in Hospitals

Stefan Russmann,[1,2] David F. Niedrig,[1,2] Gyorgy Olah,[3] and Luzi Zappa.[3] *[1]Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland; [2]Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland; [3]4solutions, Zug, Switzerland.*

Background: Pharmacotherapy in hospitals requires improved solutions for efficient and efficacious identification and prevention of clinically relevant medication errors.

Objectives: The aim of the study was to develop a solution for the analysis, prevention and outcomes research of medication errors that can be integrated into existing electronic clinical information systems.

Methods: We developed a comprehensive concept for improved hospital drug safety and implemented it as an application that features an interface with existing clinical information systems. The application uses a QLIKVIEW® platform for data visualization on desktop computers or mobile devices and was run with a pharmacoepidemiological hospital database that we had created with real-life data extracted from a clinical information system. The data covered two calendar years and approximately 500 000 patient-days and 7 million individual drug prescriptions plus laboratory results and medical diagnoses.

Results: The Drug Safety Manager (DSM) application is based on our concept of interventional pharmacoepidemiology. It enables hospitals to set up a local pharmacoepidemiological database for retrospective as well as real-time analyses of pharmacotherapy. DSM is user friendly with interactive customizable options and presents relevant safety information at a glance. Within our database, we retrospectively identified several hundred clinically relevant medication errors that can be visualized as graphs and tables or patient-level summaries. For selected targets, algorithms can generate preventive alerts and recommendations with flexible display and management options. Automated longitudinal analyses can evaluate the effectiveness of alerts over time regarding changes of prescribing behavior and monitoring.

Conclusions: DSM offers a solution for the analysis, improvement and outcomes research of hospital

pharmacotherapy and drug safety. DSM supports the reduction of clinically relevant medication errors and hospital costs related to preventable adverse drug reactions.

111. Improving Use of Medicines by Using Commitment Questions in Patient Response Forms: An Evaluation

Nicole L. Pratt, Lisa M. Kalisch Ellett, Janet K. Sluggett, Emmae N. Ramsay, Mhairi Kerr, Vanessa T. LeBlanc, John D. Barratt, and Elizabeth E. Roughead. *Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia.*

Background: Evidence from psychological studies shows that asking people to make a commitment can lead to behaviour change. These principles could be applied to interventions to improve medicines use.

Objectives: The aim of this study was to assess the impact of commitment questions on the uptake of services for improving medicines use.

Methods: Commitment questions were included in patient response forms sent for interventions targeting dose administration aids (DAAs), home medicines reviews (HMRs), diabetes services and renal function tests undertaken as part of the Veterans' MATES program. This national program delivers patient-specific prescriber feedback and tailored educational materials to patients and clinicians to improve care for Australian veterans. The questions asked if the patient intended to talk to their general practitioner (GP) about the specific issue discussed in the educational materials. Australian Government Department of Veterans' Affairs health claims data were used to assess uptake of the targeted service after each intervention. Log binomial regression models compared the monthly rate of service use in the 9 months' post-intervention among patients who answered 'yes' to a commitment question with non-responders and those answering 'no'.

Results: Each intervention targeted up to 58 000 patients. The average response rate was 28%. Positive responses were associated with a two-fold increase in uptake of DAAs (rate ratio (RR) 2.53, 95%CI 2.29–2.79; $p < 0.001$) and HMRs (RR 2.64, 95%CI 2.39–2.92; $p < 0.001$) compared with patients who did not return the response form. Positive responders were also more likely to receive diabetes care plans (RR 1.47, 95%CI 1.24–1.75; $p < 0.001$), GP management plans (RR 1.30, 95%CI 1.14–1.48; $p < 0.001$) and renal function tests (RR 1.18, 95%CI 1.13–1.24; $p < 0.001$) compared with non-responders. Similar increases in use were also observed among positive responders when compared with patients responding 'no'.

Conclusions: Positive responses to commitment questions were consistently associated with increased uptake of targeted services. Commitment questions can be incorporated into interventions to improve medicines use.

112. Retrospective Mass-Analysis of Hospital Prescription Data for Medication Errors and Subsequent Development of Highly Specific Alert Algorithms with ID PHARMA CHECK®

David F. Niedrig,[1,2] Andre Sander,[3] Daniel Diekmann,[3] and Stefan Russmann.[1,2] *[1]Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland; [2]Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland; [3]ID Berlin, Berlin, Germany.*

Background: Clinical decision support software (CDSS) identifies potential medication errors in individual patients, typically with a focus on high sensitivity but low specificity regarding clinical relevance. Our concept of interventional pharmacoepidemiology applies real-life data to retrospective analyses of medication errors in order to identify targets for highly specific alerts that can effectively prevent the most relevant medication errors.

Objectives: We aimed to identify and quantify medication errors that actually occur in clinical practice and use the results for programming CDSS alert algorithms with high specificity regarding clinical relevance.

Methods: We applied real-life data from a clinical information system of a tertiary care hospital covering one calendar year and approximately 250 000 patient-days and 3.5 million individual drug prescriptions along with laboratory results and medical diagnoses to retrospective mass-analyses using the ID PHARMA CHECK® database. Identified potential medication errors were quantified and used for the development of refined alert algorithms.

Results: ID PHARMA CHECK® identified several tens of thousands of potential drug interactions, contraindications and dosing errors and assigned them to formal severity categories. There were 3460 cases of 64 distinct formally contraindicated drug interactions. Among those we evaluated are 48 interactions as clinically relevant and suitable for display of highly specific alerts within clinical information systems; 32 alert algorithms require retrieval and implementation of current patient-specific information such as laboratory results in order to reach high specificity. The resulting algorithms were subsequently programmed for routine use with ID PHARMA CHECK®.

Conclusions: Application of CDSS to large prescription datasets can retrospectively identify medication errors and therefore play an important role for proactive quality management of pharmacotherapy in hospitals. Vice versa systematic mass-analyses of real-life data can support CDSS development with a focus on clinical relevance and efficacy.

113. Pharmacists' Perspective of Self-medication with Prescription Only Medicines, Among Patrons of Community Pharmacies in Jos, Nigeria

Maxwell Patrick Dapar,[1] Benjamin Nasara Josepth,[1] Mohammed Umar,[1] Meshak Alex Dayol,[2] and Noel Nenman Wannang.[3] *[1]Clinical Pharmacy, University of Jos, Jos, Plateau, Nigeria; [2]Pharmacy, Plateau State Specialist Hospital, Jos, Plateau, Nigeria; [3]Pharmacology Department, University of Jos, Jos, Plateau, Nigeria.*

Background: Consumption of prescription-only medicines (POMs) without professional supervision may result in considerable harm to the individuals concerned. In Nigeria, POMs are available for purchase by the public with or without prescription; hence, the prevalence of self-medication is high and is estimated to occur in 7.5% of hospitalised patients. Pharmacists with their unique expertise and easy accessibility within the community are strategic in promoting rational use of medicines. Therefore, it is necessary to investigate their views and experiences in order to gain insight and improve public health.

Objectives: The objectives of this study were to assess views and experiences of community pharmacists and to determine their attitudes towards self-medication with POMs among their clients.

Methods: This was a cross-sectional, descriptive survey of 120 registered community pharmacies located in Jos, Nigeria. Pre-tested questionnaires were used to collect data on views, attitudes and experiences of community pharmacists with self-medication among their clients.

Data were analysed using descriptive statistics as frequency distribution and cross-tabulation of variables of interest.

Results: A total of 84 pharmacists completed the survey. Whereas respondents generally agreed that self-medication with POMs compromised patient safety, up to 19% of them supported the supply of POMs to clients without prescription. Request for POMs without prescription in the community pharmacies surveyed ranged from 2 to 150 per week, comprising requests for malaria drugs 82%, antibiotics 61% and oral contraceptives 49%.

Conclusions: Study participants generally viewed self-medication as a patient safety risk even though many of the respondents did not acknowledge the contribution of pharmacists in encouraging the practice through the supply of POMs without prescription. It is essential to generate more evidence to guide the formulation and implementation of policies towards promotion of rational use of medicines in Nigeria.

114. Natural Behavioral Triggers of Adherence: Evidence from Time Shocks

Zirui Song,[1] Macarius M. Donneyong,[2] and Niteesh K. Choudhry.[2] *[1]Department of Medicine, Massachusetts General Hospital, Boston, MA, USA; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA.*

Background: With up to a third of medication prescriptions unfilled in the USA, non-adherence is a significant concern for physicians, payers, and policymakers. Amidst growing interest in incentives and policies that promote adherence, the potential impact of natural behavioral triggers, such as times on the calendar salient for health-seeking behavior, is underappreciated.

Objectives: We evaluated whether natural time shocks (the beginning of a week, a month, and a year) may be linked to medication adherence.

Methods: Using 2010–2013 United/Optum claims data, we identified unique US adults (ages 18 years or older) who refilled their medication in one of the

following three classes after prior discontinuation: angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) ($n = 285\,850$), statin ($n = 339\,595$), and beta-blocker (BB) ($n = 167\,068$). All were continuously enrolled at least 1 year before discontinuation, defined as not having a refill in the same drug class for 90 days. We compared the proportions of medication reinitiations by days of the week, days of the month, and months of the year.

Results: In our weekly analysis, 19.0% of individuals who restarted an ACE inhibitor or ARB did so on Mondays or Tuesdays, compared with 16.7% on Wednesdays or Thursdays ($p < 0.001$). Similarly, this comparison was 19.0 versus 16.8% for statins ($p < 0.001$), and 19.0 versus 16.6% for BBs ($p < 0.001$). Over a calendar year, 18.7% of restarts occurred in January or February compared with 17.4% in March or April ($p < 0.001$). This was also consistent for statins (18.4 vs. 17.1%, $p < 0.001$) and BBs (18.3 vs. 17.3%, $p = 0.006$). There was no significant predominance of restarts at the start of a month across any of the three drug classes.

Conclusions: We found a significant link between medication restarts and the beginning of a week and a year, potentially suggestive of a psychological component of health-seeking behavior prevalent at the beginning of a new time period ("turning over a new leaf"). A naturally occurring propensity for medication reinitiation at certain predictable times on the calendar may be meaningful to physicians, insurers, and policymakers who design and implement policies aimed at adherence.

115. Gender Differences in Early Access to Medicines: The Case of Diabetes Trials

Yaser T. Bazargani, Anthonius deBoer, Hubert G. M. Leufkens, and Aukje Mantel-Teeuwisse. *[1]Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Faculty of Science, Utrecht, The Netherlands.*

Background: Gender differences in access to medicines have been debated for a long time. Recent evidence does not point towards a systematic bias against women in daily practice. However, little is known about early access to medicines (e.g. in clinical trials).

Objectives: We studied gender differences in inclusion in clinical trials using diabetes as a case study.

Methods: A cohort of all clinical studies for diabetes registered in 'clinical trials.gov' with start date between 1 January 2010 and 1 January 2015 was studied. Studies were excluded if they were not interventional, did not include medicines as main intervention, were carried out in healthy volunteers and were gender specific (e.g. gestational diabetes) and if there were no data on the base line characteristics. In each study, the number of men and women enrolled was recorded and compared. The data were also classified for type of diabetes, (clinical) study phase, and funding (industry funded vs. others). Non-parametric Wilcoxon signed rank test was used for statistical analysis.

Results: A total of 197 clinical studies were included. Participation of male subjects was significantly higher than women (median % included men 55.2%, interquartile range 49.4–65.0%, $p < 0.001$). The median pairwise difference (MPD) between genders (male–female) was 10.5%. The difference was attributable to type 2 diabetes studies (MPD 9.6%, $p < 0.001$) as opposed to type 1 diabetes studies (MPD -1.3%, $p = 0.836$). The difference was statistically significant across all clinical phases ($p < 0.020$) as well as in industry (only) funded studies (MPD 9.6%, $p < 0.001$).

Conclusions: Despite all the efforts made, a difference between genders in early access to medicines under development could be observed. However, the gap was not substantial in the majority of the cases studied. The fact that industry-funded studies were experiencing a gender discrepancy warrants further research.

116. Compliance to National Directives from the French Ministry of Health for the Control of Antibiotic Utilization in Healthcare Organizations of Paris City and Inner Suburbs

Jean-Frederic Westphal. *Health Agency for Paris Region/Ministry for Health, Paris, France.*

Background: Every healthcare organization (HO) in France, except psychiatric HO, must produce a computer-based annual report in the field of antibiotic utilization (AU) control activities to the French Ministry for Health. This report consists of a number of predefined items that the physician responsible for the hospital infection control has to fill online. A scoring computer program operates at the end of the process.

Objectives: The aim of the study was to review the scores obtained in AU control activities by all the HO in Paris city and inner suburbs in 2014.

Methods: Evaluation of the reports was performed by the Health Agency for Paris region, a dependency of the French Ministry for Health. The evaluation data included the global score (decreasing from A to E) and the numerical scores recorded in the three sections (organization of control activities, means involved and actions carried out) structuring AU control activities in the report. Each section composed a number of items, which were also examined.

Results: The annual reports of 188 HO (comprising 43 051 full-time hospitalization beds) were examined, including 31 university hospitals (UH), 38 general hospitals (GH), 67 private clinics (PC), and 52 rehabilitation facilities (RF). Global scores for AU control activities in HO were as follows: A, 52%; B, 31%; C, 11%; D, 4%; and E, 2%. The highest global score A was found in around 50% of the HO, whatever the category considered. Numerical scores in the sections organization, means and actions were maximal in, respectively, 61%, 3% and 2% of UH; 63%, 18% and 13% of GH; 65%, 15% and 30% of PC; and 61%, 27% and 11% of RF. Compliance to directives was perfectible mostly for the items dealing with the means dedicated to control activities: for example, less than 50% of UH, GH or PC had a computerized physician drug-order entry system, and only 50% of RF and 62% of PC had an infectious disease specialist with regularly updated competence.

Conclusions: Review of AU control activities in the 188 HO of Paris and inner suburbs shows that there is room for improvement, especially in those activities dedicated to prevention of misuse of antibiotics.

117. Regional and Setting Variation of Antipsychotic Prescribing to Elderly Patients Across Ontario

Mina Tadrous,[1,2] Diana Martins,[2] Zhan Yao,[2] Kimberly A. Fernandes,[2] Nathan Herrmann,[3] David N. Juurlink,[2,3] Muhammad M. Mamdani,[1,2] and Tara Gomes.[1,2] *[1]Li KaShing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Sunnybrook Research Institute, Toronto, ON, Canada.*

Background: Antipsychotic drug use in elderly patients has increased over the past 10 years, raising concern of inappropriate use and associated risks of morbidity and mortality. Discussions on a provincial level have been ongoing to improve use of this drug class in the elderly. A better understanding of the prevalence and variation of antipsychotic use will inform planning initiatives on how to address this issue.

Objectives: This study aims to assess regional variation in the utilization of antipsychotic medications among elderly patients in Ontario.

Methods: We conducted a cross-sectional study to assess variation in the prevalence of use of antipsychotic medications in patients aged 65 years and older using Ontario Drug Benefits claims data in 2013. Rates were calculated based on Local Health Integration Network (LHIN) region across the province and stratified by living status (community versus long-term care (LTC)). All rates were age and sex adjusted and stratified by LHIN.

Results: We identified 109 538 elderly users of antipsychotics in 2013, 29% of whom were LTC residents. LTC users were older compared with community users, with an average age ranging from 82.6 to 84.6 years of age, compared with community users whose age ranged from 75.8 to 77.9 years of age. The majority of patients were women in both LTC (69.4% to 65.7%) and community (61.8% to 57.3%). LTC rates of antipsychotic use varied by up to 37%, ranging from 378 to 518 per 1000 elderly LTC residents depending on the geographic region. In the community, rates were lower and varied by up to 50%, ranging from 32 to 48 per 1000 elderly community residents.

Conclusions: The results demonstrate a large variation in the utilization of antipsychotics among elderly patients across regions in Ontario. This substantial variation was seen in both LTC and community settings. The use of antipsychotics is a complex issue that needs a multifaceted approach to optimal utilization. This information can be used to inform LHIN-specific approaches to optimize utilization.

118. Effect of Florida's Prescription Drug Monitoring Program and Pill Mill Law on Opioid Prescribing and Utilization

Matthew Daubresse,[1] Lainie Rutkow,[2] Hsien-Yen Chang,[2] Daniel Webster,[2] Elizabeth Stuart,[1,2] and G. Caleb Alexander.[1] *[1]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public*

Health, Baltimore, MD, USA; [2]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

Background: Prescription drug monitoring programs (PDMPs) and pill mill laws are among the principal means states use to reduce prescription drug abuse and diversion, yet there is little evidence regarding their effect.

Objectives: The aim of this study was to quantify the effect of Florida's PDMP and pill mill law on overall and high risk opioid prescribing and utilization.

Methods: We applied comparative interrupted time series analyses to IMS Health LifeLink data to characterize the effect of PDMP and pill mill law implementation on prescribers, pharmacies and patients between July 2010 and Sept 2012 in Florida (intervention state) compared with Georgia (control state). We examined outcomes including total opioid volume, average morphine-equivalent dose, average monthly days supply per transaction and average monthly prescriptions dispensed. In sensitivity analyses, we varied the length of observation and modified requirements for continuous patient observation.

Results: From July 2010 to September 2012, a cohort of 2.6 million patients, 431 890 prescribers and 2829 pharmacies were associated with approximately 480 million prescriptions in Florida and Georgia, 7.7% of which were for opioids. Average monthly opioid volume, dose per transaction, days supply and prescriptions dispensed were each higher in Florida than Georgia prior to policy implementation. Overall, Florida's laws were associated with statistically significant declines in opioid volume (3.7 kg/month, equivalent to approximately 750 000 5-mg tablets of hydrocodone) and morphine-equivalent dose (0.46 mg/month), without any change in days supply or total number of prescriptions dispensed. Twelve months following implementation, the policies were associated with an approximate 4.8% decrease in total opioid volume and 6.4% decrease in morphine-equivalent dose per transaction. Reductions were limited to prescribers and patients with the highest baseline opioid prescribing and utilization.

Conclusions: Florida's PDMP and pill mill laws were associated with modest decreases in opioid volume and dose. Decreases were greatest among prescribers and patients with highest opioid prescribing and utilization at baseline.

119. Prescription Drug Monitoring Program and Drug Arrests in Florida: Spatial Analysis

Juan M. Hincapie Castillo. *Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA.*

Background: The prescription drug monitoring program (PDMP) in Florida was created in 2009 to collect and store prescribing and dispensing data for controlled substances (Schedules II–IV). Comprehensive county-level dispensing data collected in the system offer an opportunity to evaluate the prescription rates geographically and study their association with various socioeconomic outcomes such as drug-related arrests.

Objectives: The aims of this study were to analyze the geographical distribution of controlled substances dispensed across counties in Florida and to evaluate the association between the number of drug-related arrests (all drugs) and number of controlled substances dispensed per county.

Methods: We employed a cross-sectional design using county-level prescription dispensing data provided in the Florida PDMP annual report and all county-level drug-related arrests from the Uniformed Crime Report system of the Florida Department of Law enforcement. GIS techniques were used for disease mapping, creation of suitability models and clustering analyses. A negative binomial model was fitted to evaluate the association of number of arrests to the number of prescriptions controlling for median age of the county residents.

Results: Spatial evaluation reveals a wide variability in the number of controlled substances prescribed per county. Some counties ($n = 31$) had an increase in prescription rates while the PDMP was operational, while others did not. Controlled substance prescription rates were not associated with drug-related arrests ($p = 0.34$). A Hot Spot Analysis showed that there might be disproportionate higher numbers of drug-related arrests in Calhoun, Gulf, and Miami-Dade counties.

Conclusions: There was not a significant association between the number of prescriptions and number of drug-related arrests; nevertheless, an analysis on arrests specific to drug diversion activities should be conducted to better evaluate this association.

120. The 2010 FDA Drug Safety Recommendations and LABA Dispensing Pattern Changes in Adult Asthma Patients During 2003–2012

Esther H. Zhou,[1] Elizabeth M. Kang,[1] Sally Seymour,[2] Margie Goulding,[1] and Solomon Iyasu.[1] *[1]Office of Surveillance and Epidemiology, Food and Drug Administration, Silver Spring, MD, USA; [2]Office of New Drugs, Food and Drug Administration, Silver Spring, MD, USA.*

Background: In 2010, the FDA issued Drug Safety Communications (DSCs) recommending the safe use of long-acting beta2-adrenergic agonist (LABA) products in asthma treatment.

Objectives: This study tested the hypothesis that LABA dispensing patterns would change in alignment with those recommendations.

Methods: We examined the new LABA dispensing pattern changes, with a focus on the three recommendations in the 2010 DSCs: I, single ingredient (SI) LABA use without an asthma control medication (ACM) is contraindicated; II, LABA should only be used when asthma is not adequately controlled on inhaled corticosteroids (ICS)/ACM; and III, discontinue LABA use when asthma control is achieved.

Results: Among approximately 6 million asthma patients, 477 922 adults (18–64 years old) were LABA initiators during 2003–2012 in IMS health claims data. Among any LABA initiators, the proportion of patients initiating a SI-LABA who did not have same day dispensing of an ACM decreased over the study period (p-value < 0.001); in addition, the concurrent use of ACM with SI-LABA (having overlapping therapy days on both drugs) increased. For recommendations II and III, we could not measure "asthma control" directly. The proportion of asthma patients who were dispensed an ICS within 6 months before initiating a LABA decreased from 11% to 7% (p-value < 0.001). The proportion of incident LABA patients who had >2 months LABA treatment episode increased over the study period.

Conclusions: The significant decrease in SI-LABA initiation is consistent with FDA's recommendations. Low dispensing of ICS/ACM prior to LABA initiation may suggest patients were put on LABA without a trial of ICS/ACM.

121. Hospital Discharge Medicines Information: From Trial to Policy

Alice V. Gilbert,[1,2] Michael Roberts,[2,3] Des Williams,[3] and Andrew L. Gilbert.[3] *[1]Pharmacy, Top End Health Service, Darwin, Northern Territory, Australia; [2]School of Medicine, University of Queensland, Brisbane, Queensland, Australia; [3]Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia.*

Background: Poor clinical handover of medicines information for patients leaving hospital is a major healthcare problem. Pharmacists at a tertiary teaching hospital in Australia have been providing a Medicines Information Transfer Fax (MITF) as part of their clinical service. Owing to patient/pharmacist ratio, this service cannot be provided to all patients; thus, it is targeted on those at highest risk. This study is part of a health service review to improve the transfer of medicines information. The first study demonstrated that pharmacists provide timely and accurate information to primary healthcare professionals. This study is the next stage in the development of a multidisciplinary medicines discharge policy.

Objectives: The aim of the study was examine patient prioritisation by pharmacists when providing an MITF to inform policy development and direct clinical services.

Methods: A random sample of 99 patients who had an MITF completed by a pharmacist in April to September 2014 were selected. Patients were reviewed against items in the 'Safety and Quality Risk Stratification tool' and the 'Society of Hospital Pharmacists Australia patient risk stratification instrument' to determine if a patient prioritisation strategy was used by the pharmacists.

Results: We selected 99 patients. Twenty were excluded: 11 did not have a hospital discharge summary, five had no prescription found at time of study and four did not use the standard MITF template. All 79 remaining patients met at least one of the eight high-risk criteria for medication misadventure; 78 (98%) had co-morbidities, 76 (97%) had changes to their regular medication, 72 (91%) were on five or more medicines, 62 (78%) had compliance or adherence issues, 44 (56%) were elderly, 32 (41%) had renal/liver impairment, 20 (25%) had dose to change post discharge and 4 (0.05%) were confirmed/suspected medication-related admissions. Fifty-five (70%) patients met five or more high-risk criteria.

The pharmacists in this study were appropriately prioritising patients to receive an MITF.

Conclusions: Two to three percent of all hospital admissions in Australia are medication related. MITF is now embedded within this hospital. Policy development will commence, based on these results, to ensure MITF is a core responsibility by clinical pharmacists.

122. Diabetes Secondary Prevention: Are We Getting the Right Services to the Right People at the Right Price?

Eric Romo, Kate L. Lapane, Aimee R. Kroll-Desrosiers, and Allison B, Rosen. *Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA.*

Background: Secondary prevention among diabetics provides an excellent case study of whether US physicians are providing value-conscious care. Such care would target therapies to those who would benefit most and prescribe the lowest-cost alternative among therapies with comparable health benefits. Two equally effective therapies—angiotensin converting-enzyme inhibitors (ACE) and the far more expensive angiotensin receptor blockers (ARB)—reduce cardiovascular disease (CVD) events among diabetics, but to a far greater extent in those at high CVD risk.

Objectives: The aims of the study were (i) to determine whether ACE/ARB use increased more rapidly in high-risk compared with low-risk patients, suggesting physicians recognize the importance of targeting high-risk patients, and (i) to determine whether ACE use increased more than ARB use, suggesting physicians recognize that the lower-cost alternative of two equally effective therapies should be chosen.

Methods: We identified 2453 participants of National Health and Nutrition Examination Survey ≥ 55 years who self-reported diabetes (representing 10.08 million US adults). Respondents were categorized as high-risk if albuminuria or pre-existing CVD was present. ACE/ARB use was determined by interviewer review of current medications. Multivariable analyses of trends in ACE/ARB use (overall and stratified by high/low risk) provided estimates adjusted for demographic changes over time (1999–2010).

Results: Among older diabetics, the prevalence of ACE/ARB use increased from 43.6% in 1999–2002 to 65.3% in 2007–2010. However, use increased far more among the low-risk group (37.1%) than the high-risk group (23.5%). The increase in ACE/ARB use was entirely due to increased use of the more expensive ARBs. Further, the increase in ARBs was greatest in those least likely to benefit; ARB use increased threefold in the high-risk group and sevenfold in the low-risk group ($p < 0.001$ in both).

Conclusions: ACE/ARB use by adult diabetics has increased over time in the USA. However, the increases have paradoxically occurred to a greater extent among those least likely to benefit and with those therapies that increase cost without providing additional clinical benefit.

123. Evaluation of Antimicrobial Stewardship Programs in Makkah Region Hospitals, Kingdom of Saudi Arabia

Abdul Haseeb,[1] Mohamed Azmi Ahmed Hassali,[2] Abdulrahman Bakhsh,[3] Hani Saleh Faidah,[4] Waleed Hassan Almalki,[1] and Mahmood Essam Uddin El Raggal.[1] *[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [2]Department of Social Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia; [3]Department of Emergency Medicines, Ajyad Emergency Hospital, Holy Makkah, Saudi Arabia; [4]Faculty of Medicines, Umm Al Qura University, Holy Makkah, Saudi Arabia.*

Background: Antimicrobial resistance is a significant and growing threat to public health owing to increased mortality, morbidity, and costs. This is due to irrational and excessive use of antimicrobials in hospital settings where the intensity of use of antimicrobial prescribing is high. Implementation of antimicrobial stewardship programs in healthcare settings is an important tool to prevent antimicrobials' negative consequences.

There is limited information on effective 'Antimicrobial Stewardship Programs' (ASP) established in the Kingdom of Saudi Arabia. To the best of our knowledge, there is no literature that describes the proportion of healthcare institutions with ASP Makkah-wide, except for some studies performed in Riyadh region of Saudi Arabia regarding the assessment of consumption of antibiotics in order to highlight the importance of antimicrobial stewardship programs in the Kingdom.

Objectives: The aim of this study was to identify various types of antimicrobial stewardship programs implemented in Makkah region hospitals and their perceived success.

Methods: We have conducted a survey of Makkah hospitals to determine the existence of antimicrobial stewardship programs, perceived success of these activities, perceived barriers to implementation, and outcome measures routinely monitored.

Results: Responses were received from 19 (68%) directors of pharmacies from all hospitals. The types of antimicrobial stewardship programs are identified as administration related, antimicrobial use and prescribing related, education and training related, and infection control and surveillance related. Most common types of strategies were formulary restrictions (90%) for broad-spectrum antimicrobials and use of automatic stop orders (65%) to limit empirical therapy of antimicrobials. Majority of the hospitals lacked local antimicrobial guidelines (90%) based on hospital-wide antibiograms.

Conclusions: Information from this survey will be used to develop Standards of Practice for Antimicrobial Stewardship applicable to the Makkah healthcare setting, which indirectly promotes rational antimicrobial use.

124. Proton Pump Inhibitors—Should More Care Be Taken with Prescribing for Older Women?

Susan E. Tett,[1] Marielle M.C. van der Hoorn,[2] Annette J. Dobson,[3] and Geeske G.M.E.E. Peeters.[3,4] *[1]School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia; [2]Faculty of Medicine, VU University Amsterdam, Amsterdam, The Netherlands; [3]School of Population Health, The University of Queensland, Brisbane, QLD, Australia; [4]School of Human Movement Studies, The University of Queensland, Brisbane, QLD, Australia.*

Background: Many prescribed drugs are continued into old age, but the balance of risks and benefits may be altered. The proton pump inhibitors (PPIs) are one example. Older women have higher bone fracture risk than younger and perhaps should not be commonly exposed to PPIs (increased fractures reported as an adverse effect).

Objectives: The aim of this study was to examine the use of PPIs and the association between PPI use and subsequent use of anti-osteoporosis medication (AOM) in older women.

Methods: Use of PPIs (>1 dispensing 2003–2010) and subsequent use of AOMs, as an indicator of at-risk bone health, was assessed in the older age cohort of the Australian Longitudinal Study on Women's Health. The women, born 1921–1926 (age 76–81 years in 2002), had linked administrative dispensing data (national Pharmaceutical Benefits Scheme).

Results: Overall, 1432 out of 3082 in the elderly female cohort (47%) used PPI in the 8-year period. Of the 1432 PPI users and 1650 PPI non-users, 488 (34%) and 375 (23%) became AOM users, respectively. PPI use was associated with an increased risk of subsequent AOM use (sub-hazard ratio [SHR] = 1.40; 95%CI 1.20–1.63). Number needed to harm (NNH) (inverse of absolute risk) was 8.8; so an additional one in every nine PPI using women (>75 years old) would subsequently receive AOM in an 8-year period, in comparison with those not receiving a PPI. After adjustment for confounders, the association remained significant (SHR = 1.33, CI = 1.13–1.55). Analysis with PPI categorized according to defined daily dose showed no evidence for a dose–response effect. Analysis by type of PPI showed an increased risk for AOM use after use of rabeprazole (SHR = 1.93, CI = 1.28–2.92), esomeprazole (SHR = 1.73, CI = 1.29–2.32) or >1 type of PPI over time (SHR = 1.84, CI = 1.49–2.28).

Conclusions: A high proportion (47% over the 8-year period) of an elderly (>75 years old) female cohort was exposed to PPI medication. PPI users were at higher risk of subsequently using AOM, with a relatively low NNH of 8.8. Rabeprazole and omeprazole were associated with higher risks. Thus, for women over 75 years, a reappraisal of the risks of fracture may be needed when considering use of a PPI.

125. Metformin Utilization Patterns in Pediatric Population Aged 10–19 years in the US: 2009–2013

Tongtong Wang, Ann Marie McNeill, Yong Chen, and Ravi Shankar *Merck & Co., Inc., Kenilworth, NJ, USA.*

Background: Metformin is the only oral antihyperglycemic agent approved for use in the pediatric patients with type 2 diabetes mellitus (T2DM). It

may also be used to treat other conditions, such as hyperinsulinemia, pre-diabetes, and polycystic ovarian syndrome (PCOS). Therefore, an assessment of the prevalence of T2DM in the pediatric population based on the utilizations for metformin may overestimate the burden of the disease. However, metformin utilization patterns in the pediatric population remain unclear.

Objectives: The aim of this study was to assess metformin utilization patterns in pediatric patients in the USA from 2009 through 2013.

Methods: We used annual data from the National Disease and Therapeutic Index (NDTI), an ongoing office-based physician survey conducted by IMS Health (Plymouth Meeting, Pennsylvania) that provides national-level estimates of disease and treatment patterns occurring in physician offices. Drug-use frequency and reasons for uses (i.e., therapeutic indications) of single-ingredient metformin for pediatric patients 10–19 years of age between 2009 and 2013 were extracted and analyzed. Descriptive statistical analysis was used to examine changes in the number of and reasons for metformin use over the 5-year period.

Results: Metformin use by physicians for pediatric patients has decreased by 42.8% from 2009 to 2013 (from 217 716 in 2009 to 124 386 in 2013). The most common reason metformin was used was diabetes (34.9%), followed by metabolic syndrome (25.5%), PCOS (17.2%), and obesity (6.5%). Metformin utilization pattern remained stable between 2009 and 2013.

Conclusions: Diabetes only accounted for approximately a third of the total metformin use in pediatric population aged 10–19 years. Other indications included metabolic syndrome, PCOS, and obesity. Despite the NDTI's limitations arising from sampling and data collection methodologies, our study still provides useful insights into metformin utilization pattern among pediatric population. Caution should therefore be exercised when utilizing metformin prescription as a proxy measure to estimate the burden of T2DM in the pediatric population.

126. The Irrational Use of Antibiotics in Sudan

Isam Eldin Mohammed Ali Mustafa. *Pharmaceutical Services, National Health Insurance Fund, Khartoum, Sudan.*

Background: The irrational use of medicines is a common problem worldwide. Recent literature revealed that more than 50% of all medicines are prescribed inappropriately, which results in serious public health problems like antimicrobial resistance. However, the extent of irrational antibacterials at National Health Insurance Fund (NHIF), Sudan. is not well identified

Objectives: The aim of this study was to determine the pattern of antibacterial medicines prescribing at primary healthcare facilities of NHIF, Sudan.

Methods: The study followed the method developed by the WHO/INRUD. Design: We performed a retrospective study. Setting and study population: Twenty primary health centres were selected from five states that represented the five geographical regions of the Sudan, and then 2401 patients encounters were withdrawn from these centres by systematic random sampling from the year 2012. Outcome measure(s): Medicines prescribing indicators.

Results: On average, the percentage of encounters with antibacterial is 64% (ranged from 43% in patients aged over 55 years to 84% in children under 5 years old). The patient's age was negatively correlated with the percentage of encounters with an antibacterial prescribed ($r=-0.288$, $N=2270$, $p<0.01$, two tails), while there were no significant differences in prescribing behavior of doctors for men or women ($t=0.919$, $p=0.35$, two tails). The main causes of antibacterials prescribing were upper respiratory tract infections, urinary tract infections, typhoid fever and gastro-intestinal disorders. Interestingly, 45% of patients with malaria received antibacterials.

Conclusions: There is overuse of antibacterials, which reflects the urgent need for development and implementation of antibiotics policy and standard treatment guidelines especially for management of respiratory infections, urinary tract infections and typhoid fever.

127. Pharmacist-Led Educational Interventions on Antibiotics Use and Their Resistance Among Geriatric Diabetes Patients in Malaysia

Muhammad Shahid Iqbal,[1] Muhammad Waseem Iqbal,[2] Muhammad Zahid Iqbal,[1] and Mohd Baidi Bahari.[1] [1]*Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, AIMST University, Semeling, Kedah Darul Aman, Malaysia;* [2]*Faculty of Law, University of Malaya, Kuala Lumpur, Wilayah Persekutuan, Malaysia.*

Background: The report of Malaysian Statistics on Medicine 2007 showed anti-infective agents as the most frequently prescribed medicines with a 6% increase in consumption of antibiotics from 2006 to 2007. Patient-focused pharmacist-led educational interventions are vital to change patients' mindsets towards appropriate antibiotics use.

Objectives: This study is designed to investigate pharmacist-led educational interventions regarding understanding of antibiotic use, antibiotic resistance and various other correlating factors among geriatric diabetes patients in Malaysia.

Methods: A cross-sectional study was conducted on a newly developed and validated self-administered research instrument. The research instrument was developed by extensive literature review and subjected to face and content validity. A pilot study on 20 patients was conducted to ascertain the reliability coefficient of the research instrument. Data were entered to SPSS version 21.0, and descriptive and inferential statistics were applied. A p-value < 0.05 was considered statistically significant.

Results: A total of 240 diabetes patients on antibiotics participated in the study. Participants were divided into control and intervention groups, that is, 120 in each group. No significant differences were observed in either group for mean age, gender and occupation. In intervention group, a significant improvement ($p < 0.001$) in knowledge and awareness regarding the antibiotics use and resistance were observed. The control group showed inadequate knowledge regarding the antibiotics use and resistance.

Conclusions: From the obtained results of the study, it can be concluded that the general public are not fully aware of the importance of antibiotics use and their resistance. Most of the patients agreed that awareness about antibiotics appropriate use and their resistance knowledge will have a positive impact on their quality of health. Educating general public regarding the antibiotics use and resistance can inculcate awareness toward the judicious use of antibiotics, which can serve to eradicate antibiotic resistance.

128. Prescribing Quality of Antimalarial Medicines in Sudan: A National Study at National Health Insurance Fund in 2013

Isam Eldin Mohammed Ali Mustafa. *Pharmaceutical Services, National Health Insurance Fund, Khartoum, Sudan.*

Background: The burden of malaria-related morbidity and mortality is high worldwide especially in developing countries. However, the number of cases of malaria in Sudan was reduced dramatically during the last 10 years owing to the effective national malaria programme. The malaria medicines are availed by The Global Fund free of charge, but the prescribing of medicines should be according to the national protocol of the management of malaria. The adherence of medical doctors to the national protocol of malaria in Sudan was not assessed.

Objectives: The aims of this study were to assess the prescribing pattern of antimalarial medicines and to identify the extent of the adherence of medical doctors to the national protocol of management of malaria.

Methods: Setting and study population: Twenty primary health centres were selected from five states that represented the five geographical regions of the Sudan, and then 2401 patients encounters were withdrawn from these centres by systematic random sampling.

Results: On average, the percentage of encounters with antimalarial medicines is 15.6%, with 12.6% out of the lab. Results were positive; 39.6% of malaria-confirmed cases were treated by artemether injection, while 53% of cases diagnosed as malaria clinically (negative lab results) received artemether injection, which is against the management protocol. The most patients categories received antimalarial medicines were the poor families and self-employed; 45% of patients with malaria had been prescribed at least one antibiotic.

Conclusions: There is poor adherence to the national protocol of management of malaria at primary healthcare facilities, which may result in development of resistance to antimalarial medicines, poor health outcomes and waste of resources. Training of medical doctors and clinical supervision are needed to improve the adherence to the protocols.

129. Evaluation of Vancomycin Pharmacokinetics in Coronary Care Units, Kingdom of Saudi Arabia

Abdul Haseeb,[1] Abdulrahman Bakhsh,[2] Hani Saleh Faidah,[3] Aljoharh Abdulrahman Alziady,[1] Walaa Dhaifallah Alnemari,[1] Marwah Hassan Mustafa Barnawi,[1] Rozan Mohammed Radwan,[1] and Mahmood

Essamuddin El Ragal.[1] [1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Saudi Arabia;* [2]*Department of Emergency Medicine, Ajyad Emergency Hospital, Ministry of Health, Holy Makkah, Saudi Arabia;* [3]*Faculty of Medicines, Umm Al Qura University, Holy Makkah, Saudi Arabia.*

Background: Dosing for narrow therapeutics ranged drugs should be based on pharmacokinetics parameters and must be according to patient characteristics and patient current medications therapy and disease status.

Vancomycin is a life-saving drug in case of severe infectious diseases and must be dosed appropriately as per patient characteristics and disease status. Despite being a correct choice for specific organisms, underdosing may lead to disease exacerbations resulting to negative consequences. In addition, overdosing might result in a toxic range and can cause severe nephrotoxicity and ototoxicity. In both scenarios, there is a need for application of pharmacokinetics and pharmacodynamics principles to promote rational use and prevent the risk of dosing errors.

Objectives: The purpose of this study was to assess vancomycin dosing pattern and its association with patient characteristics.

Methods: This retrospective study was carried out in a coronary care unit of two critical care settings in order to evaluate dosing pattern and its association with digoxin toxicity.

Results: A total of 26 patients charts were reviewed retrospectively from two intensive care units to find out a relationship between patient characteristics, for example, age, weight and kidney function with dosing pattern. Mean age of patients studied was 63 years; 46% patients were men and 54% were women. Severe pneumonia (70%) was the primary reason for vancomycin use among patients. Most of the patients (35%) were maintained on 500 mg/hourly maintenance dose. Interestingly, 65% of the patients were on furosemide therapy while on vancomycin therapy.

Conclusions: Our results concluded that use of therapeutic drug monitoring was very rare among patients while prescribing vancomycin and suggested application of clinical pharmacokinetics services in healthcare settings to promote patients safety in critical care settings.

130. Antimicrobial Prescribing Pattern for Upper Respiratory Tract Infections in Ambulatory Care Settings, Kingdom of Saudi Arabia

Abdul Haseeb,[1] Abdulrahman Bakhsh,[2] Muhammed Tarique Imam,[1] Jehan Rostom,[1] Shahd Khan,[1] Shehana Aljarbou,[1] Rehab Alotaibi,[1] Amal Alotaibi. [1]*Department of Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Saudi Arabia;* [2]*Department of Emergency Medicine, Ajyad Emergency Hospital, Ministry of Health, Holy Makkah, Saudi Arabia.*

Background: Overuse and inappropriate antimicrobial prescribing may lead to antimicrobial resistance as a result and must be addressed and prevented through appropriate strategies. Inappropriate use includes use of wrong antibiotics, and incorrect dosage and duration of therapy as per patient characteristics. Upper respiratory infections are most frequent reason for ambulatory care visits, and excessive antibiotics prescribing for such infections may lead to high risk of antimicrobial resistance. Patterns of antibiotic use in acute respiratory tract infections should be documented from ambulatory care clinics in order to develop appropriate strategies to prevent resistance rate in a community.

Objectives: The main goal of this study is to assess antimicrobial prescribing pattern for upper respiratory tract infections (URTIs).

Methods: This retrospective study was conducted in a secondary care hospital in Makkah, and handwritten prescriptions from ambulatory care settings were assessed during 2 month's period in order to access antimicrobial prescribing pattern for acute respiratory tract infections.

Results: A total of 612 orders were evaluated retrospectively to study prescribing pattern. Mean age of patients was 41 years. Most common reason of antimicrobial prescribing was for sore throat (49%) and common cold (11%). Amoxicillin (Keflex 250 mg) was the first most prescribed drug for URTI followed by augmentin (7%), clarithromycin (7%) and cephalexin (3%), respectively. Average antibiotics per prescription were 2. Average duration of the treatment was 5 days' regimen.

Conclusions: There must be appropriate strategies to discourage antimicrobial prescribing for upper respiratory tract infection owing to their viral reasons. Our results serve as baseline data and provide further

insight into planning and development of antimicrobial prescribing for URTIs.

131. First-Line Therapy of Metastatic Colorectal Cancer in Elderly Patients: Experience of a French Centre

Amaury Daste,[1] Pernelle Noize,[2] Magali Rouyer,[3] Eric Terrebonne,[1] Alain Ravaud,[4] Annie Fourrier-Réglat,[5] Denis Smith.[1] *[1]CHU de Bordeaux, Bordeaux, France; [2]CHU de Bordeaux, Inserm U657, Inserm CIC1401, Bordeaux, France; [3]Inserm CIC1401, ADERA, Bordeaux, France; [4]Université de Bordeaux, CHU de Bordeaux, Inserm CIC1401, Bordeaux, France; [5]Université de Bordeaux, CHU de Bordeaux, Inserm U657, Inserm CIC1401, Bordeaux, France.*

Background: Although metastatic colorectal cancer (mCRC) is frequent in elderly patients, they are under-represented in clinical trials, especially of targeted therapies (TT) now recommended in first-line therapy in combination with cytotoxic drugs.

Objectives: The aim of this study was to evaluate the use of TT and cytotoxic drugs in first-line therapy of mCRC in elderly patients.

Methods: A retrospective cohort was conducted in a French teaching hospital. Patients aged ≥75 years seen for decision of first-line therapy of mCRC from 2008 to 2012 were included and followed up until progression, death or last consultation. Data were collected from medical files and compared between treated and untreated patients and then between two treatment groups: TT combined with cytotoxic drugs (TT group) versus only cytotoxic drugs (no-TT group). Median progression-free survival (PFS) and median overall survival (OS) were estimated in each treatment group after exclusion of patients who had a metastasectomy after first-line.

Results: Seventy-five patients were included (median age 81 years; 34.7% women). Nine patients (12.0%) had an oncogeriatric consultation and 12 (16.0%) no specific treatment. Older age ($p = 0.002$), Eastern Cooperative Oncology Group (ECOG) > 2 ($p < 0.001$), mobility disorders ($p < 0.001$) and cognitive disorders ($p = 0.002$) were more frequent in untreated patients. Among 57 patients who received one of the treatment options defined earlier, 33 were in the TT group (57.9%). The TT (75.8% bevacizumab; 24.2% cetuximab) was combined with a polychemotherapy in 87.9% of patients. Older age ($p = 0.01$), ECOG > 2 ($p < 0.001$) and hypertension ($p = 0.04$) were more frequent in the no-TT group. At baseline, a dose reduction was more often performed in the no-TT group (83.3% vs. 60.6%; $p = 0.06$). Adverse events (AE) occurred more frequently in the TT group (30.3% with ≥2 AE vs. 12.5%; $p = 0.05$). Median PFS and OS were 10.3 and 15.1 months in the TT group versus 3.6 and 8.6 months in the no-TT group.

Conclusions: In clinical practice, few elderly mCRC patients have an oncogeriatric evaluation. Patients receiving TT are selected and represent less than half of elderly patients seen for decision of first-line therapy. This could be improved with more oncogeriatric evaluations.

132. Oncopharmacoepidemiology: 10-Year Experience of a French Research Platform

Pernelle Noize,[1] Magali Rouyer,[2] Angela Grelaud,[2] Cécile Droz,[2] Régis Lassalle,[2] Jérémy Jové,[2] Marie-Agnès Bernard,[2] Amandine Gouverneur,[3] Pauline Bosco-Lévy,[4] Julien Bezin,[3] Denis Smith,[5] Alain Ravaud,[6] Nicholas Moore,[3] Annie Fourrier-Réglat.[3] *[1]CHU de Bordeaux, Inserm U657, Inserm CIC1401, Bordeaux, France; [2]Inserm CIC1401, ADERA, Bordeaux, France; [3]Université de Bordeaux, CHU de Bordeaux, Inserm U657, Inserm CIC1401, Bordeaux, France; [4]Université de Bordeaux, CHU de Bordeaux, Bordeaux, France; [5]CHU de Bordeaux, Bordeaux, France; [6]Université de Bordeaux, CHU de Bordeaux, Inserm CIC1401, Bordeaux, France.*

Background: Historically, pharmacoepidemiological studies related to oncology were focused on cancer risk with exposure to medicines. Since a decade, the marketing of targeted therapies (TT) gives opportunities for research centered on anticancer drugs.

Objectives: The aim of the study was to describe the experience of the Bordeaux Pharmacoepi research platform (registered with ENCePP) in the evaluation of use and effectiveness of anticancer drugs in real-life practice.

Methods: Since 2004, the platform enabled to perform field and database studies. Four multicenter cohorts of new users of TT in various cancers were conducted. Patients were identified using hospital pharmacy dispensations or prescribers. Detailed data were collected through on-site hospital chart review. Patients were

followed up at least 2 years to evaluate progression-free survival (PFS; progression as reported by physicians) and overall survival (OS). Stratified analyses were performed to compare use and effectiveness between elderly and younger patients. Drug utilization studies were conducted using the permanent sample of the national healthcare insurance database (EGB), especially on oral anticancer drugs in breast cancer.

Results: Nearly 2000 patients were included in cohorts (28–92 centers): 793 users of bortezomib in multiple myeloma, 411 of bevacizumab, 389 of cetuximab in colorectal cancer and 302 of sunitinib in renal cell carcinoma. In all cohorts, PFS and OS were close to those reported in clinical trials. Elderly patients treated with bortezomib, bevacizumab or cetuximab had similar survival outcomes than younger patients despite different comorbidities or treatment patterns. Among 600 women initiating hormonal therapy for breast cancer identified through EGB, more than 40% were non-persistent at 5 years.

Conclusions: Available data from the platform give an interesting and reassuring insight of effectiveness of TT. Results suggest a channelling of TT to patients with better health status; further cohorts of patients newly diagnosed with cancers must be implemented to better understand treatment determinants and study comparative effectiveness between TT. Studies on adherence to oral drugs and long-term safety studies are also needed.

133. Utilisation and Safety of Deferasirox (Exjade®): Results from an Observational Cohort Study in England

Vicki Osborne,[1,2] Miranda Davies,[1,2] Deborah Layton,[1,2] and Saad A. W. Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK.*

Background: Deferasirox is an oral iron chelating agent (ICA) primarily used to reduce chronic iron overload in patients (pts) receiving blood transfusions for various chronic anaemias and some non-transfusion dependant anaemias. Use in patients 2 years+ is licensed for certain indications. An identified safety concern is increased serum creatinine (Cr) during treatment (Rx); monitoring is therefore recommended prior to and during Rx.

Objectives: The aim of this study was to examine the utilisation and safety of deferasirox used in general practice in England.

Methods: We performed a single exposure observational cohort study. Pts were identified from dispensed prescriptions for deferasirox. Prescriptions were collected from September 2006 to September 2014. Outcome data were collected via postal questionnaires sent to prescribers ≥6 months after first dispensed prescription, including information on prior Cr measurements and prior use of alternative ICAs. Summary descriptive statistics were calculated.

Results: Evaluable cohort = 122 pts (2–17 years = 51, 41.8%); median age = 23 years [interquartile range (IQR) 11–61]; 58.2% male. Frequent reasons for prescribing (underlying conditions leading to iron overload) are as follows: sickle cell anaemia (27/103 where specified, 26.2%) and beta thalassaemia (BT) (26, 25.2%); 53.8% BT pts had frequent blood transfusions (≥7 ml/kg/month packed red blood cells). Most pts (43/51, 84.3%) were prescribed licensed doses of 10 or 20 mg/kg/day at start. Rx was initiated by a specialist for 100 pts (100/103, 97.1%). Eighteen serum Cr values were reported prior to Rx, four in excess of reference range [median value of all prior serum Cr 69 μmol/L (IQR 51–95)]. Events reported in these four pts included raised ferritin and renal function decline. In total, 91 incident events were reported, including two raised serum Cr after starting Rx; 45.6% pts (26/57) used an alternative ICA in the 12 months prior to Rx; 80.8%, desferrioxamine.

Conclusions: These results show that deferasirox is largely being prescribed for its licensed indications in general practice in England, and events reported were consistent with the known safety profile. These results contribute to post-marketing information. However, considering the small cohort size, any conclusions from this study should be put into context with results from other studies.

134. Anticoagulant Treatment After VTE in the Netherlands

Irene D. Bezemer,[1] Elsa J. van den Berg,[1] Kerstin Folkerts,[2] Luke Bamber,[2] Fernie J. A. Penning-van Beest,[1] Michiel Coppens,[3] Ron M. C. Herings.[1] *[1]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [2]GHEOR General Medicine, Bayer HealthCare Pharmaceuticals/Bayer Pharma AG, Wuppertal, Germany; [3]Department of*

Vascular Medicine, Academic Medical Center Amsterdam, Amsterdam, The Netherlands.

Background: Adequate initial anticoagulant treatment of venous thromboembolism (VTE) can prevent recurrences and death. Guidelines for anticoagulant treatment balance the risks of recurrence and bleeding based on underlying risk factors.

Objectives: The aim of this study was to describe initial anticoagulant treatment after VTE as recorded in electronic healthcare records and relate this to the underlying risk factors, guidelines and recurrence rates.

Methods: From the PHARMO GP Database, patients with deep venous thrombosis (DVT) or pulmonary embolism (PE) in 2007–2011 were identified for whom out-patient pharmacy dispensing data were available. Cancer, other risk factors, and type and duration of anticoagulant treatment (low-molecular-weight heparin (LMWH) and/or vitamin K antagonist (VKA)) within 90 days of diagnosis and recurrence of VTE were assessed.

Results: The study cohort included 1581 VTE patients: 1053 with DVT and 528 with PE. For 70–86% of the VTE patients, dispensings of anticoagulant treatment were observed within 90 days. The median duration of anticoagulant dispensings when both LMWH and VKA dispensings were observed was 3.5 months among patients with provoked VTE and 3.7 months among patients with unprovoked VTE. In the provoked and unprovoked VTE cohorts, the observed median dispensing duration of (initial) LMWH treatment was 0.4 months (about 12 days) for patients who also received VKA. Recurrent VTE occurred mostly after discontinuation of anticoagulant treatment. Longer dispensing durations were observed among patients without recurrence.

Conclusions: Treatment after VTE as captured in observational healthcare data generally follows the Dutch guidelines. However, many patients received LMWH dispensing covering periods longer than 2 weeks. Furthermore, among patients with a VTE recurrence, shorter duration of anticoagulant treatment was observed compared with patients without a recurrence.

135. Antihypertensive Drug Use and Blood Pressure Control in Nigeria

Onyinye O. Akunne, and Aduragbenro D. Adedapo. *Pharmacology and Therapeutics, University of Ibadan, Ibadan, Oyo, Nigeria.*

Background: Drug use studies carried out from time to time promote rational drug use, especially in patients with chronic diseases.

Objectives: The aim of this study was to evaluate antihypertensive medication use pattern and BP control among hypertensive patients in Nigeria.

Methods: This study was carried out in out-patient clinics of a tertiary hospital in Nigeria between November 2011 and April 2012. All patients diagnosed of hypertension with or without co-morbidity/complications such as diabetes, renal diseases, cerebrovascular disease and other cardiovascular diseases prior to study period were included. Age, sex, blood pressure result and anti-hypertensive prescription were obtained from patient's medical record; duplication of cases was avoided. Systolic blood pressure (BP) and diastolic BP readings $<130/140$ mmHg and 80/90 mmHg in patients with/without complication were considered controlled. Antihypertensive drugs were grouped accordingly as angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), centrally acting adrenergic drugs, beta-blockers (BB), calcium channel blockers (CCB), and diuretics (D). Prescribed doses were compared with daily defined dose (DDD). Independent-sample t test and bi-variate correlation were used to compare means and test for association.

Results: Among 1891 patients prescribed antihypertensive drugs (mean age, 60; 58% women), D were most commonly prescribed either as mono-therapy or in combination ($n=1435$ [30.6%]), followed by CCB ($n=1258$ [26.8%]), ACEI ($n=988$ [21.1%]), centrally acting adrenergic drugs ($n=428$ [9.1%]), ARB ($n=295$ [6.3%]) and BB ($n=279$ [6.0%]). BP was controlled in 43.0% patients. Those receiving less than three drugs had significantly better BP control than those receiving three or more drugs. Presence of co-morbidity/complication (42% of cases) was not associated with number of drugs prescribed. Although prescription pattern was similar across ages, diastolic BP control declined with increasing age ($r=-0.261$, $p<0.01$). DDD was exceeded in 49% of prescribed drugs.

Conclusions: Although diuretics were more prescribed, BP control was low. Switching between antihypertensive drug classes to achieve optimum BP control should be encouraged rather than polypharmacy and dose increments.

136. Impact of Comorbid Diabetes Mellitus on Adjuvant Chemotherapy Selection in Older Rectal Cancer Patients

Phyo T. Htoo,[1] Hanna K Sanoff,[2] and Jennifer L. Lund.[1] [1]*Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA;* [2]*Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Clinical guidelines recommend adjuvant chemotherapy for stage II and III rectal cancer patients following neoadjuvant chemoradiation (CRT) and surgery with either 5-fluorouracil (5FU) alone or in combination with oxaliplatin. Diabetes mellitus (DM) may influence chemotherapy selection owing to the overlapping risk of peripheral neuropathy with DM and oxaliplatin.

Objectives: We examined the impact of DM on the choice of adjuvant therapy (5FU alone or in addition to oxaliplatin) in a cohort of older rectal cancer patients.

Methods: We identified newly diagnosed non-metastatic rectal cancer patients aged 66+ years from 2004 to 2009 who underwent neoadjuvant CRT, surgery and adjuvant chemotherapy using Surveillance, Epidemiology and End Results program Medicare data. Pre-existing DM, other comorbidities and patient and tumor characteristics were assessed during 1 year prior to cancer diagnosis, and adjuvant chemotherapy receipt was ascertained in the 120 days post-surgery. Relative risks (RRs) for receipt of oxaliplatin versus 5FU alone were estimated using multivariable binomial regression, adjusting for measured confounders.

Results: The study included 630 patients; 126 (20%) had DM at the baseline and 331 (53%) received oxaliplatin. The chance of receiving oxaliplatin was lower in patients with prior DM compared with those without DM (46% vs. 54%) (adjusted RR = 0.92, 95%CI: 0.75, 1.12). The receipt of oxaliplatin in diabetics was slightly lower among those 66–74 years old (RR = 0.89 with 95%CI: 0.70, 1.11) compared with those over 75 years old (RR = 0.93, 95%CI: 0.61, 1.42). The association was stronger among patients with pathologic stage III disease (RR = 0.76, 95%CI: 0.54, 1.07), while RR for lower staged tumor patients was null (RR = 1.03, 95%CI: 0.79, 1.33).

Conclusions: Although there is little evidence to suggest oxaliplatin neurotoxicity is increased in patients with DM, the lower oxaliplatin use in diabetics, after adjusting for patients' comorbidities and demographics, show that DM may influence treatment decisions. While the association does not differ much by age, tumor stage appears to be an important consideration along with DM in the chemotherapy selection.

137. An Investigation of the Concomitant Use of Angiotensin-Converting Enzyme Inhibitors, Non-steroidal Anti-inflammatory Drugs and Diuretics in Romania

Camelia Bucsa,[1] Daniela C. Moga,[2,3] Andreea Farcas,[1] Cristina Mogosan,[1] Dan L. Dumitrascu.[4] [1]*Drug Information Research Center, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania;* [2]*Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky, Lexington, KY, USA;* [3]*Department of Epidemiology, College of Public Health, Lexington, KY, USA;* [4]*2nd Department of Internal Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Cluj, Romania.*

Background: Despite the positive effects of angiotensin-converting enzyme inhibitors (ACE-I), there are still concerns and challenges regarding adverse drug reactions, especially renal failure and hyperkalemia.

Objectives: Using retrospective data, our objectives were to determine the prevalence of co-prescribing of ACE-I with non-steroidal anti-inflammatory drugs (NSAIDs) and ACE-I/NSAIDs with diuretics at hospital discharge and to identify factors associated with co-prescribing. Secondary, we evaluated the extent of serum creatinine and potassium monitoring in patients treated with ACE-I and these associations and determined the prevalence of values above the upper normal limit (UNL) in monitored patients.

Methods: Hospitalized patients with ACE-I in their therapy at discharge were included in three groups, as follows: ACE-I, DT (double therapy with ACE-I and NSAIDs) and TT (triple therapy with ACE-I, NSAIDs and diuretics) groups. We evaluated differences on demographic characteristics, co-morbidities, medications and laboratory monitoring and quantified the patients with serum creatinine and potassium levels above the UNL using descriptive statistics. Logistic regression analysis with backward elimination was performed to identify significant predictors of combination therapy.

Results: Of 9960 admitted patients, 1214 were prescribed ACE-I, 40 were prescribed ACE-I/NSAIDs and 22 were prescribed ACE-I/NSAIDs/diuretics (3.13% and 1.72%, respectively, of the patients prescribed with ACE-I). Serum creatinine and potassium were monitored for the great majority of patients from all groups. The highest percentage of hyperkalemia was found in the DT group (10% of the patients) and of serum creatinine above UNL in the TT group (45.45%). The logistic regression final model showed that younger patients and monitoring for potassium were significantly associated with combination therapy.

Conclusions: The prevalence of patients receiving DT/TT was relatively low, and their monitoring during hospitalization was high. Factors associated with combination therapy were age and testing for serum potassium during the hospital stay.

138. Evaluating Prescriber Concordance with Prescribing: Results from a Post-marketing Study

Deborah Layton,[1,2] Naseer Qayum,[1] Claire Doe,[1] Shayne Freemantle,[1] Saad A. W. Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK.*

Background: At launch (2005), ivabradine (Procoralan©) was indicated for treatment of chronic stable angina pectoris in patients (pts) with normal sinus rhythm, with a contraindication (CaI)/intolerance for beta-blockers. A drug utilisation study was conducted to support risk management of the drug. Study objectives include examining CaI, warnings for use (WFU) and incidence of two adverse events: visual phosphenes (phos) and bradycardia (brad) (persistent heart rate < 50 bpm).

Objectives: The aims of this study were to develop a tool to support assessment of prescribing discordance with recommendations and explore impact on phos and brad incidence.

Methods: We performed an observational single exposure cohort study. Exposure data were collected from dispensed prescriptions (Rx) from November 2005 to May 2009; outcome data (including pre-existing pt medical conditions/drugs, which carried CaI/WFU) from forms sent to physicians (general practitioners) ≥6 months after each pt's first Rx. An algorithm-based prescribing framework was developed and assisted with the assessment of available information according to CaI/WFU in SPC. To explore impact of prescriber discordance, phos and brad risk (%) and 95%CI were calculated by group (≥1 CaI; ≥1 WFU; both CaI/WFU; concordant or unknown). Descriptive statistics were calculated.

Results: The final cohort was 4624, with median age of 68 years (interquartile range 60, 77); 57% (2663) were male. CaI/WFU were assessed for 3357 pts: 74% (2491) were concordant, 21% (701) had WFU, 4% (124) had CaI and 1% (41) had both CaI/WFU. Brad was reported for 96/4624 pts (2.1% (1.6, 2.5)); 73 were assessed: 4/124 pts (3.2% (0.9, 8.3) were CaI, 17/701 (2.4% (1.4,3.9)) had WFU, 1/41 had both CaI/WFU and 51/2491 pts (2.0 (1.5, 2.7)) were concordant. Phos was reported for 140/4624 pts (3.0% (2.5, 3.6)); 104 were assessed: 2/124 pts (1.6% (0.2, 5.8)) were CaI, 23/701 had WFU (3.3% (2.1, 4.9)), 1/41 had both CaI/WFU, and 78/2491 (3.1% (2.5, 3.9)) were concordant.

Conclusions: In this study, the incidence of brad and phos was common in all concordance groups, although estimates lacked precision. This study demonstrates the feasibility of using a framework to assess prescribing discordance as reported in drug utilisation studies to identify at-risk populations, which may help support post-marketing risk : benefit evaluations.

139. Effect of Hospital Admission on Antihypertensive Medication Utilization Among Older Persons

Tariq M. Alhawassi,[1,2] Ines Krass,[2] and Lisa G. Pont.[3] *[1]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia; [3]Sydney Nursing School, The University of Sydney, Sydney, New South Wales, Australia.*

Background: Hospitalization may impact long-term medication use, yet little is known about the impact of hospitalization on antihypertensive therapy and blood pressure control in older persons.

Objectives: The aims of this study were to explore changes to long-term antihypertensive medication regimens following hospitalization and identify factors associated with regimen changes.

Methods: A retrospective cross-sectional survey in a large metropolitan teaching hospital was conducted. A systematic sample of all patients aged ≥65 years admitted between 1 January and 31 December 2010 were included. Antihypertensive medication use and BP control on admission and discharge were compared for patients with hypertension. Factors associated with changes to antihypertensive regimens were identified using multifactorial logistic regression analysis.

Results: Of the 503 patients in the cohort, 69.0% (347) had a documented diagnosis of hypertension, and 88.8% of those with hypertension were using antihypertensive medications prior to hospitalization. Changes to antihypertensive medications occurred in 39.5% ($n = 135$) of patients with hypertension. On discharge, the proportion of patients with hypertension who were receiving an antihypertensive agent had declined compared with admission (85.3% vs. 89.0%, $p < 0.0001$). Adverse drug reactions (OR = 5.0, 2.80–9.34) were the main documented reasons for changes to antihypertensive medications. Use of beta blockers prior to admission (OR = 2.1, 1.08–4.00) or a history of myocardial infarction (OR = 2.09, 1.07–3.79) was also associated with antihypertensive medication changes.

Conclusions: Hospitalization has a significant impact on antihypertensive pharmacotherapy. Two out of every five older persons on antihypertensive medications will experience changes to their regimens during admission to hospital. Communication regarding medication changes is essential to ensure quality health care.

140. Concomitant Prescription of QT-Prolonging Drugs in Dronedarone Users

Chuntao Wu,[1] Andrew Koren,[2] Jane Thammakhoune,[1] Hayet Kechemir Kechemir,[3] Stephanie Tcherny-Lessenot,[3] Stephen Lin,[1] and Juhaeri Juhaeri.[1] *[1]Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, USA; [2]Cardiovascular Medical Unit, Sanofi, Bridgewater, NJ, USA; [3]Global Pharmacovigilance and Epidemiology, Sanofi, Chilly-Mazarin, France.*

Background: Drugs that prolong the QT interval and that might increase the risk of torsade de pointes are contraindicated against use with dronedarone. This contraindication is included in the dronedarone prescribing information and risk evaluation and mitigation strategy communication plan.

Objectives: The aim of this study was to estimate the prevalence of concomitant prescription of potent QT-prolonging drugs in dronedarone users.

Methods: The Clinformatics DataMart and the MarketScan databases were used separately to identify two cohorts of patients prescribed dronedarone between July 2009 (launch date in US) and December 2013. For each cohort, the prevalence of concomitant prescription for QT-prolonging drugs within 30 days before or after initiation or refilling of dronedarone was calculated. The prevalence of prescription of QT-prolonging drugs excluding antiarrhythmics (amiodarone, dofetilide and sotalol) was also calculated because the prescriptions of antiarrhythmics most likely reflected switching between dronedarone and these drugs.

Results: There were 9575 and 46 759 dronedarone users identified in Clinformatics and MarketScan between July 2009 and December 2013, respectively. During the study period, the respective prevalences of concomitant prescription for any QT-prolonging drugs within 30 days before or after initiation/refilling of dronedarone were 18.1% (95% confidence interval (CI): 17.3–18.8%) in Clinformatics and 16.8% (95% CI: 16.5–17.1%) in MarketScan. Amidodarone, sotalol and dofetilide were the most frequently prescribed QT-prolonging drugs; and the respective prevalences of concomitant prescription for these drugs were 9.3%, 5.7% and 1.7% in Clinformatics and 9.5%, 4.7% and 1.0% in MarketScan. Excluding antiarrhythmics, the respective prevalences of concomitant prescription of QT-prolonging drugs were 2.5% (95%CI: 2.2–2.8%) in Clinformatics and 2.6% (95%CI: 2.4–2.7%) in MarketScan.

Conclusions: In the dronedarone users identified in two claims databases in the USA, the prevalence of concomitant prescription of QT-prolonging drugs excluding antiarrhythmics was low, implying low prevalence of actual concomitant use of such drugs with dronedarone.

141. Aspirin and Risk of Cancer Among French Population: A Population Based Cohort Study

Aya Ajrouche,[1,2,3] Candice Estellat,[1,2,3] Carine Roy,[1,2] David Hajage,[1,2,3] Marie Dalichampt,[4] Florence Tubach.[1,2,3] *[1]Center of Pharmacoepidemiology of the AP-HP, AP-HP, Bichat-Claude Bernard Hospital, Paris, France; [2]CiC-EC 1425, UMR1123, INSERM, Paris, France; [3]ECEVE, UMR1123, Sorbonne Paris Cité University, Paris, France; [4]CNAMTS, Paris, France.*

Background: Cancer is a worldwide burden of disease in terms of morbidity, mortality and cost. Selective secondary analyses of cardio-vascular RCT have suggested a 30% cancer risk reduction after 5 years of aspirin treatment.

Objectives: The aim of this study was to evaluate whether a long-term aspirin treatment at low dose could be protective against cancer among French population.

Methods: An 8 years' historical cohort was conducted using the Echantillon Généraliste de Bénéficiaires (permanent sample of the French national health insurance information system) and looking for the incidence of cancer in exposed and non-exposed group. Patients included had at least 1 year of follow-up before inclusion to exclude all prevalent cancer and aspirin exposure. Exposure to aspirin was defined as filling at least two dispensing for aspirin at antiplatelet dose (<325 mg/day) over six consecutive months. Exposure was modelled as a time-dependent variable: patients will not be exposed from the time of study entry until the sixth month after their second dispensed treatment and exposed from this date until the end of follow-up (time of the earliest of the following events: death from any cause or end of the observation period on 1 January 2014). Cox proportional hazards time-dependent models with age as timescale and adjusted for sex, comorbidities and co-treatment were undertaken. Smoking status was not available.

Results: Among 124 005 individuals included in the study, 15 648 verified exposure criteria. There were 1390 (8.9%) incidents cancers in exposed group versus 13 689 (12.63%) in the unexposed group. After multivariable adjustment, low-dose aspirin was not associated with a decreased risk of any of the site-specific cancers or cancer in general (HRa 1.06; 95%CI, 0.99–1.12). However, an increased risk of death was observed in the exposed group (HRa 1.67; 95%CI, 1.58–1.77).

Conclusions: Low-dose aspirin was not associated with a decreased risk of cancer. Concurrent risk of death may have influenced our results; therefore, a multi-state model taking into account all competing risk such as major bleeding, cardiovascular events, cancer and death have to be developed.

142. Drug Utilization Patterns of Azilsartan Medoxomil in Primary Care Setting in Germany

Birgit Ehlken,[1] Margarita Shlaen,[1] Juliana Rex,[2] Paul Dolin.[3] *[1]Real World Evidence Solutions, Epidemiology and Safety, IMS Health, Munich, Germany; [2]Real World Evidence Solutions—LifeLink, IMS Health, Frankfurt/M, Germany; [3]Pharmacoepidemiology, Takeda Development Centre Europe, London, UK.*

Background: Azilsartan medoxomil (AM), an angiotensin II receptor blocker, is indicated for the treatment of hypertension. This study was undertaken to gain real-world data on prescribing patterns in a European setting.

Objectives: The aims of this study were to describe the population being prescribed AM and to evaluate drug utilization in the primary care setting since the product launch in Germany.

Methods: A cohort study design was implemented using longitudinal patient-centric anonymized electronic medical records data for Germany (IMS Disease Analyzer). The study population included patients with at least one prescription of AM (ATC code C09CA09) from January 2012 to December 2013 and activity in the database at least 12 months before and 6 months after exposure start. The statistical analysis was performed descriptively.

Results: In total, 1159 patients prescribed AM were identified; 852 patients (73.5%) fulfilled the inclusion criteria and were eligible for analysis. About 50% were male. The mean age was 64.5 (SD 12.6) years; the proportion of elderly (at least 75 years) was 15% and 30% of male and female users, respectively. Only one patient was aged less than 18 years old. The majority of patients (83.1%) had essential hypertension (ICD-10 code I10), 4.1% had other diagnoses (including other forms of hypertension), and for the remaining 12.4%, indication for the first AM prescription was not recorded. There were no cases of use initiated in patients with heart failure in the absence of hypertension. Less than 1% had co-morbidity with severe renal impairment and 5% with hepatic impairment. Simultaneous co-prescription of at least one other antihypertensive drug was identified in 23.0% of AM users, and overlapping prescription with other antihypertensive drugs in 67.8% of AM users. The simultaneous co-administration of at least one drug that could in theory result in a drug interaction was recorded in 2.8% of AM users; co-administration with a direct renin inhibitor (aliskiren) was uncommon (0.5% of AM users).

Conclusions: The study provides real-world data on the utilization of AM in the primary care setting in

Germany. The study found good compliance with product labelling information.

143. Association Between Analgesic Use and Daytime Sleepiness in People with and Without Dementia in Aged Care Facilities

Edwin C. K. Tan,[1] Renuka Visvanathan,[2] Sarah N. Hilmer,[3] Agnes Vitry,[4] and J. Simon Bell.[1,4] *[1]Centre for Medicine Use Safety, Monash University, Parkville, VIC, Australia; [2]School of Medicine, University of Adelaide, Adelaide, SA, Australia; [3]Sydney Medical School, University of Sydney, Sydney, NSW, Australia; [4]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia.*

Background: Managing pain in residents of aged care facilities is challenging, especially for people with dementia. Clinicians must weigh the benefits of analgesic use against the potential for adverse events, particularly daytime sleepiness.

Objectives: The aim of this study was to investigate the association between analgesic use and daytime sleepiness in residents with and without dementia in Australian aged care facilities.

Methods: A cross-sectional study of 383 residents with and without dementia from six aged care facilities in South Australia was conducted. Analgesic use in the previous 24 hours (paracetamol, opioid and non-steroidal anti-inflammatory drugs (NSAID)) was the primary exposure and daytime sleepiness (Epworth Sleepiness Scale $\geq$ 10) was the primary outcome. Covariates included insomnia, depression, Charlson's comorbidity index, sedative load, pain and dementia severity. Study nurses administered validated and dementia-specific scales. Medication use data were extracted directly from each resident's medication chart. Logistic regression was used to compute adjusted odds ratios (AORs) and 95% confidence intervals (95%CIs) for factors associated with daytime sleepiness.

Results: In the previous 24 hours, analgesics were used by 288 (75.2%) residents. The most prevalent analgesics were paracetamol (264 [68.9%]), opioids (76 [19.8%]) and NSAIDs (14 [3.7%]). Overall, 116 (30.3%) residents reported having daytime sleepiness. Of the residents with dementia (n = 169, 44.1%), 77 (45.6%) reported having daytime sleepiness. Opioid use in the previous 24 hours was not associated with daytime sleepiness in residents with and without dementia. Paracetamol use was positively associated with daytime sleepiness in residents without dementia (AOR 3.15; 95%CI 1.05–9.54). However, there was no significant association between paracetamol use and daytime sleepiness in residents with dementia (AOR 2.03; 95%CI 0.85–4.82).

Conclusions: Although daytime sleepiness occurs in a large number of residents, especially those with dementia, this sleepiness is not necessarily associated with opioid use. The risk of opioid-induced sleepiness appears to be managed by preferential prescribing of paracetamol to residents at risk of daytime sleepiness.

144. Potential for Underdosing of Antipsychotics (AP) in Primary and Mental Health Care: Findings from Post-authorisation Safety Studies Conducted on Seroquel XL©

Deborah Layton,[1,2] Vicki Osborne,[1,2] Miranda Davies,[1,2] Ian Ratcliffe,[1] Sarah Clarke,[1] Saad A. W. Shakir,[1,2] Joe Reilly,[3] Tony Hale.[4] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK; [3]Centre for Integrated Health Care Research, Durham University, Stockton on Tees, County Durham, UK; [4]University of Kent, Canturbury, Kent, UK.*

Background: UK guidelines state that the lowest possible dose of antipsychotics should be used and titrated to the lowest effective dose. The Risk Management Plan for quetiapine extended release (Seroquel XL©) had a need to describe utilisation in primary care in all indications (via Modified Prescription-Event Monitoring (MPEM)-12 months' observation (obs)) and in the mental health setting in patients (pts) with schizophrenia (Schiz) or bipolar disorder (BD) (via specialist cohort event monitoring (SCEM)-12 weeks' obs; ENCePP Study reg. 5412). Study objectives included exploring posology.

Objectives: The aim of this study was to describe dosing of Seroquel XL©, with a focus on potential for underdosing.

Methods: Exposure, selected prior medical history (pmh) and medications use data were collected for each study from forms sent to hospital specialists for SCEM December 2009 to December 2012 and to

primary care physicians (general practitioner (GPs)) for MPEM September 2008 to February 2013, respectively. Descriptive statistics were calculated; doses were converted to % of relevant max dose by indication and titration stage in SPC—underdosing defined as <100%).

Results: In the M-PEM (13 276), potential underdosing was very common; start: Schiz: 37% (785/2136); BD: 3% (98/3500); major depressive disorder (MDD): 6% (147/2646); maint: Schiz: 38% (509/1339); BD: 33% (721/2165); MDD: 32% (531/1648). In the SCEM (869), potential underdosing was also very common at start: Schiz: 56% (144/258); BD: 59% (204/305) and at maint (86% (223), and 91% (315), respectively).

Conclusions: Both studies found that potential underdosing occurred for all indications. Start dose data correlated poorly with SPC and expert guidelines to use lowest effective dose but corresponded to UK prescribing guidelines, which do not recommend excessive doses, unless other evidence-based strategies have failed. Possible explanations for more common potential underdosing in SCEM versus MPEM is that pts treated by specialists may require more individualised therapy (including use of immediate release quetiapine) to initially stabilise their condition, whilst GPs tend to manage pts at later stages. Further work will explore impact of age and prior/concurrent psychotropic use on underdosing.

145. Factors Associated with High Anticholinergic Burden in Aging Adults with Intellectual Disabilities: A Cross-sectional Study

Maire O'Dwyer,[1] Ian Maidment,[2] McCallion Philip,[3] McCarron Mary,[4] Henman Martin,[5] Kathleen Bennett,[6] Jure Peklar.[7] *[1]IDS-TILDA, Trinity College Dublin, Dublin, Ireland; [2]School of Life and Health Sciences, Aston University, Birmingham, UK; [3]Centre for Ageing and Community Wellness, University at Albany, New York, USA; [4]School of Pharmacy and Pharmaceutical Sciences, Trinitry College Dublin, Dublin, Ireland; [5]Dean of Health Sciences, Trinity College Dublin, Dublin, Ireland; [6]Department of Pharmacology and Therapeutics, Trinity Centre for Health Science, Dublin, Ireland; [7]Faculty of Pharmacy, University of Ljubljana, Slovenia.*

Background: Anticholinergic (AC) medications are associated with cognitive and functional decline in older people, with risk of adverse outcomes increasing with increasing AC exposure. Older people with intellectual disabilities are at increased risk of high AC exposure owing to higher prevalence of multimorbidity, particularly psychiatric morbidities.

Objectives: The aims of this study were to determine individual's AC exposure using the AC cognitive burden (ACB) scale, identify therapeutic classes contributing to burden and determine clinical and demographic factors associated with two levels of AC exposure (ACB score 1–4, ACB 5+).

Methods: Cross-sectional (self-report/proxy report) medication data were drawn from Wave 1 of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing, a study on ageing of 753 nationally representative people with ID aged over 40 randomly selected from the National Intellectual Disability Database. Medication data were available for 736 (98%). Each individual's cumulative AC exposure was calculated using the ACB. Multinomial logistic regression was performed identifying clinical and demographic factors associated with ACB score 1–4, and ACB 5+.

Results: In the eligible population of 736 participants (mean (±SD) age 54.1 (±8.8) years,55% female), 522 (70.9%) were exposed to an ACB medicine (ACB 1+); 214 (29%) had an ACB score of 5+; mean total ACB score = 4.5 (±3.0). Antipsychotics accounted for 35.6% of the cumulative ACB score. Age over 65 years was associated with increased likelihood of both levels of AC exposure (ACB 1–4—adjusted OR 3.28; 95% CI 1.49–7.25, ACB 5+—adjusted OR 3.08; 95%CI 1.21–7.63) and having a mental health condition (ACB 1–4—adjusted OR 9.79; 95%CI 5.63–17.02, ACB 5+—adjusted OR 23.74; 95%CI 12.29–45.83).

Conclusions: Using a simple cumulative measure proved an effective means to capture total burden and established that AC exposure was high and associated with older age and mental health morbidity. This highlights need for comprehensive medication reviews for older people with intellectual disabilities.

146. Use of Benzodiazepines in Combination with Other Addictive Drugs

Christian Berg, Svetlana Skurtveit, Solveig Sakshaug, Vidar Hjellvik, and Marte Handal. *Department of Pharmacoepidemiology, Norwegian Institute for Public Health, Oslo, Norway.*

Background: Combined use of various addictive drugs may increase the risk of adverse effects. Co-medication with two benzodiazepines (BZDs) and BZDs combined with z-hypnotics and opioids are not recommended according to common treatment guidelines.

Objectives: The aim of this study was to study the level of co-dispensing of other addictive drugs in BZD users.

Methods: Data on BZD, z-hypnotics, and opioids dispensed to all adult outpatients in Norway (aged 18 and over) in 2013 were obtained from the Norwegian Prescription Database. Co-dispensing on the same date of z-hypnotics, opioids and two or more BZDs to BZD users in 2013 was recorded. Palliative care patients were excluded.

Results: The number of users of BZD in 2013 was 263 471 (1 year prevalence 6.2%). The highest proportion of co-dispensing on the same day was BZD and z-hypnotics ($n = 58\,949$, 22.4%), followed by BZD and opioids ($N = 48\,666$. 18.5%). Two or more BZDs were dispensed to 5.3% ($N = 11\,141$) of the BZD users, and a combination of BZDs, z-hypnotics and opioids on the same day was dispensed to 4.2% ($N = 13\,854$) of the BZD users.

Conclusions: Dispensing on the same day of various addictive drugs most likely indicates concomitant use. The finding in this study demonstrates a substantial proportion of not recommended prescribing of addictive drugs.

147. Patterns and Predictors of Persistent Opioid Use Following Hip or Knee Arthroplasty

Seoyoung C. Kim, Jessica M. Franklin, Katsiaryna Bykov, Huichuan Lii, Michael A. Fischer, Niteesh K. Choudhry, and Brian T. Bateman. *Brigham and Women's Hospital, Boston, MA, USA.*

Background: Joint arthroplasty is often recommended in patients with severe osteoarthritis when medical treatment cannot adequately control joint pain and function. Some patients, however, continue to use opioids even after joint arthroplasty.

Objectives: The aim of this study was to examine the risk, patterns and predictors of persistent opioid use after hip or knee arthroplasty.

Methods: Using claims data (2003–2011) from a US commercial health plan, we identified a cohort of adults who underwent hip or knee arthroplasty and filled at least one opioid prescription within 30 days after the surgery and followed them up for 1 year from the 30th postoperative day. We required continuous enrollment for at least 365 days prior to and 360 days after the beginning of follow-up. Group-based trajectory models examined the patterns of opioid use in the year following the surgery. Multivariable logistic regression was used to determine preoperative predictors of persistent opioid use (C-statistics = 0.91).

Results: There were a total of 37 468 patients who underwent hip or knee arthroplasty; 47% were 60 years or older, 56% female and 52% used opioids prior to the surgery. In the year after undergoing hip or knee arthroplasty, 6.4% ($n = 2383$) had persistent opioid use. Persistent opioid users were more likely to be age < 50 (multivariable OR 1.7, 95%CI 1.4–2.1) versus ≥70 and to have knee arthroplasty (1.4, 95%CI 1.3–1.6) versus hip, diagnosis of back pain (1.3, 95%CI 1.1–1.4), rheumatoid arthritis (1.5, 95% CI 1.3–1.8), and use of benzodiazepine (1.4, 95%CI 1.3–1.6), and marijuana (3.2, 95%CI 1.1–9.5). Longer duration (78.8, 95%CI 64.6–96.1 for ≥7 months vs. none) of pre-operative opioid use was the strongest predictor. Other significant predictors included smoking, fibromyalgia, and use of gabapentin and antidepressants in the year prior to hip or knee arthroplasty.

Conclusions: Over 6% of patients persistently used opioids in the year after hip or knee arthroplasty. Longer duration of pre-operative opioid use, younger age, knee arthroplasty, and marijuana and benzodiazepine use were significant predictors for persistent use.

148. Description of Antiparkinsonian Drug Use in US Medicare Claims Database: A Feasibility Assessment

Catherine B. Johannes,[1] Brian Calingaert,[2] Catherine W. Saltus,[1] Sigal Kaplan,[3] Elizabeth Grubb,[4] James A. Kaye,[1] Elizabeth B. Andrews.[2] *[1]Pharmacoepidemiology and Risk Management, RTI Health Solutions, Waltham, MA, USA; [2]Pharmacoepidemiology and Risk Management, RTI Health Solutions, Research Triangle Park, NC, USA; [3]Global Patient Safety & Pharmacovigilance, Teva Pharmaceutical Industries,*

Petach-Tikva, Israel; [4]Global Health Economics and Outcomes Research, Teva Pharmaceutical Industries, Overland Park, KS, USA.

Background: Epidemiologic studies have shown an inverse association of Parkinson's disease (PD) and cancer occurrence overall, but a positive association with malignant melanoma, whether the increased risk of melanoma is due to the disease or its treatment is unknown. In preparation for a safety study of antiparkinsonian drugs (APD) and melanoma in US Medicare claims data, we conducted a feasibility assessment to evaluate potential study size and follow-up time.

Objectives: The aim of this study was to describe the characteristics of PD patients initiating APD, including uptake and utilization of rasagiline, a monoamine oxidase-B inhibitor approved in the USA in 2006, and follow-up time.

Methods: This was a descriptive retrospective cohort analysis of US Medicare claims data (2006–2011). The sample comprised individuals aged ≥65 years with fee-for-service Medicare Parts A, B and D insurance, with ≥2 outpatient/physician claims for PD (ICD-9 code: 332.0) or ≥1 inpatient claim for PD, and with first exposure to either (i) rasagiline or (ii) another APD after at least 6 months of enrollment. Characteristics of the study cohorts were compared.

Results: Compared with the other APD initiator cohort ($n = 120\,262$), the rasagiline initiator cohort ($n = 14\,170$) included on average a slightly younger population (76 vs. 78 years), a higher proportion of men (54% vs. 47%) and a lower proportion of individuals receiving a Medicare low-income subsidy (25% vs. 44%). At cohort entry, 91% of rasagiline initiators and 57% of other APD initiators had prior use of an APD other than the qualifying drug. The proportion of patients with ≥3 years of follow-up in each cohort was similar (28% to 27%). Annual losses to follow-up occurred in 10–11% of each cohort, mainly because of death.

Conclusions: With the observed uptake of rasagiline in US seniors, an estimated additional 2 years of data may be necessary before accrual of sufficient follow-up time to evaluate melanoma as an outcome and conduct comparative exposure analyses. Initial results suggest that rasagiline initiators may differ from other APD initiators and thus could affect the relative risk of melanoma.

149. Utilisation of a New Once Weekly Injection for Type 2 Diabetes Mellitus (T2DM): Interim Results from an Observational Cohort Study of Exenatide (Bydureon®) in England

Vicki Osborne,[1,2] Naseer Qayum,[1] Abigail Coughtrie,[1] Deborah Layton,[1,2] Saad A. W. Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK.*

Background: Bydureon® is indicated for the treatment (Rx) of T2DM in combination with metformin, sulfonylurea (SU), thiazolidindione (TZD) alone, metformin and SU, or metformin and TZD for patients (pts) who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies alone. A post-marketing observational cohort study of Bydureon® was requested as part of the EU Risk Management Plan. The final target cohort size is 5000 pts. This study is ongoing.

Objectives: The aim of this study was to describe the utilisation characteristics of pts prescribed Bydureon® at interim.

Methods: We performed an observational, population-based cohort design in primary care. Pts in the interim cohort were identified from all dispensed prescriptions for Bydureon® in England in September 2011 to January 2014 (interim data lock). Data were collected from prescribers via postal questionnaires sent ≥12 months after the first prescription was dispensed. Summary descriptive statistics were calculated.

Results: Evaluable cohort at interim = 520 pts; median age 58 years (interquartile range 51–65); 58.1% male. T2DM and time since diagnosis were specified for 493 pts; the majority were diagnosed >10 years prior to starting Rx (210, 42.6%). Where specified ($n = 441$), 91.1% pts were classed as obese (body mass index > 30.0 kg/m^2) immediately prior to Rx. Upon starting, 48.4% (134/277) had a HbA1c >9%, representing very poor diabetes control. Most pts had HbA1c ≥7.5% (223, 80.5%). The majority of pts used 2 mg once weekly (489/492, 99.4%), and most pts were prescribed Bydureon® as either second line (158/477, 33.1%) or third line co-therapy (307, 64.4%). The majority of pts were prescribed Bydureon® with metformin (417/520, 80.2%). Co-prescribing of insulin was also reported (117, 22.5%)

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Conclusions: These interim results characterise the utilisation of Bydureon® in primary care in England. The majority of pts had T2DM, used 2 mg once weekly and were co-prescribed metformin. Most pts were obese, which raises the possibility of channelling by prescribers owing to the purported benefits of Bydureon® in weight loss. This interim analysis will be superseded when validation and follow-up are complete for the final analysis.

150. Withdrawn by author

151. Utilisation of Asenapine in the Mental Health Care Setting in England and Wales: First Results from a Specialist Cohort Event Monitoring (SCEM) Study

Vicki Osborne,[1,2] Jan Slade,[1] Deborah Layton,[1,2] Saad A. W. Shakir,[1,2] Joseph Reilly.[3] *[1]Drug Safety Research Unit, Southampton, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK; [3]Durham University, Durham, UK.*

Background: OBSERVA is a specialist cohort event monitoring (SCEM) study being conducted as part of the EU Risk Management Plan to monitor the short-term safety and utilisation of asenapine prescribed to new user patients (pts) by psychiatrists in the mental health care setting in England and Wales

Objectives: The aim of this study was to describe utilisation characteristics of pts prescribed asenapine at interim and assess use in relation to the license

Methods: We conducted a single exposure observational cohort of pts prescribed asenapine over 3 years. Pts were identified via network of psychiatrists in collaboration with Mental Health Research Network. Data are abstracted from medical records. After pt consent, questionnaires completed by study investigators collect baseline data incl. exposure and 12 weeks' post-index date outcomes. At interim, pts were recruited from 14 National Health Service trusts from February 2013 to February 2014 (interim data lock). Descriptive statistics were calculated (% specified, excl. missing).

Results: Interim cohort = 57 consented pts, of which 46 pts were evaluable with baseline data. Most frequent indication was bipolar disorder (36, 78.3%), although 10 non-licensed indications were reported (21.7%). Most frequent dose at index date was 5 mg 2× daily in 16 pts (16/46, 34.8%), whilst at maintenance, it was 10 mg 2× daily (9/42, 21.4%). Doses other than 5 or 10 mg 1× or 2× daily were reported for three pts at index (6.5%) and five pts at maintenance (11.9%). History (>28 days prior) of psychiatric conditions (suicide/self-injury and depression) was common (19/46; 41.3% and 25/46; 54.4%, respectively). History of diabetes mellitus was also common (5/46; 10.9%). Of risk factors for potential misuse at baseline, majority of pts had no prior or current history of alcohol misuse (25/45, 55.6%) or substance abuse (29/43, 67.4%).

Conclusions: The majority of new user pts at interim were treated with asenapine for licensed indications. Prior history of psychiatric conditions is as expected for populations treated for mental health conditions. Prevalence of off-label indications was common, as were risk factors for potential misuse. These interim data demonstrate the importance of SCEM to gather real-world data to support post-marketing risk : benefit management.

152. Adherence to Guidelines and the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions Criteria for Colchicine Dosing for Gout Treatment in Beneficiaries of the Nova Scotia Seniors' Pharmacare Program

Emily Black, Ingrid Sketris, Chris Skedgel, Erica MacLean, John Hanly. *Dalhousie University, Halifax, NS, Canada.*

Background: The Screening Tool of Older Person's potentially inappropriate Prescriptions criteria for colchicine in older persons (STOPP) criteria consider >3 months of treatment as potentially inappropriate. Recent evidence and guidelines suggest that low-dose colchicine has similar efficacy and less toxicity compared with high-dose colchicine in the management of acute gout.

Objectives: The aims of this study were to determine characteristics of colchicine prescriptions and to evaluate adherence to the STOPP criteria and the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines.

Methods: Nova Scotia Seniors' Pharmacare Program beneficiaries who met inclusion criteria for an incident case of gout and who filled at least one prescription for

colchicine from 1 April 2006 to 31 March 2011 were included. Data were analyzed to assess adherence to dosing recommendations by the ACR and EULAR guidelines for gout. Kaplan–Meier survival curves were generated to illustrate the proportion of beneficiaries by the duration of their treatment course. Multivariate logistic regression was used to identify predictors of the study population who made a prescription claim for colchicine >90 and >180 days. All analyses were performed using SAS/STAT software, version 9.2.

Results: From 1 April 2006 to 31 March 2011, there were 903 unique Nova Scotia Seniors' Pharmacare Program beneficiaries who met criteria for incident gout and were dispensed drug therapy for management of gout. For beneficiaries receiving colchicine therapy, the mean prescribed daily dose of colchicine over the 5-year period ranged from 1.39 to 1.50 mg. Colchicine doses >1.2 mg were prescribed in approximately a third of the study population. Colchicine was prescribed for >90 days in 14% of treatment courses and for >180 days in 8% of treatment courses. Sex was the only predictor of treatment duration >90 days.

Conclusions: This study determined that many prescriptions for colchicine did not adhere to STOPP guidelines on the duration of therapy or the ACR and EULAR guidelines on the dose of therapy.

153. Ontario MedsCheck Annual Pharmacy Medication Review Service: A Comparison Between Initial and Well Established Implementation Periods

Lisa Dolovich,[1,2] Giulia P. Consiglio,[2] Lusine Abrahamyan,[2,3] Elizabeth A. Bojarski,[2] Linda D. MacKeigan,[2] Petros Pechlivanoglou,[2,3] Nedzad Pojskic,[4] Valeria E. Rac,[2,3] Jiandong Su,[5] Murray D. Krahn,[2,3,5] and Suzanne M. Cadarette.[2,5] *[1]Department of Family Medicine, McMaster University, Hamilton, ON, Canada; [2]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [3]Toronto Health Economics and Technology Assessment Collaborative, University of Toronto, Toronto, ON, Canada; [4]Ontario Pharmacists Association, Toronto, ON, Canada; [5]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada.*

Background: A MedsCheck Annual (MCA) consultation is a government-funded, medication review service in Ontario, Canada, for people taking three or more prescription medications for chronic conditions.

Objectives: The aim of this study was to describe and compare the demographic and clinical characteristics of MCA recipients overall and in two time periods.

Methods: This cohort study leveraged linked administrative claims data from 1 April 2007 to 31 March 2013. Two time periods were considered: (i) 1 April 2007 to 31 March 2008, the first year of MCA service, and (ii) 1 April 2012 to 31 March 2013, the most recent year with complete data available. Ontario Drug Benefit (ODB) patients were eligible for MCAs since 1 April 2007, and on 17 July 2007, MCA eligibility was extended to Ontarians taking three or more prescription medications for chronic conditions. Descriptive statistics of MCA recipients were calculated overall and over the two time periods and stratified by age.

Results: The MCA service was provided to 1 498 440 Ontarians (55% seniors, 55% female), and 36% of recipients had two or more MCAs overall. Service provision increased over time with a sharper increase after 2010. From 2007 to 2008, MCA was provided to 194 726 Ontarians (67% over age 65) and in 2012–2013, 372 054 Ontarians (44% over age 65). In 2007–2008, more recipients lived in urban centres (91%) versus 2012–2013 (86%). The proportion of ODB recipients with high medication costs in the prior year decreased from 14% in 2007–2008 to 4% in 2012–2013. Diagnoses of hypertension (76% in 2007–2008 and 60% in 2012–2013), chronic obstructive pulmonary disease or asthma (34% in 2007–2008 and 29% in 2012–2013) and diabetes (40% in 2007–2008 and 22% in 2012–2013) were most common. In 2007–2008 versus 2012–2013, more Ontarians were taking antihypertensives, diuretics and narcotics prior to receiving MCA.

Conclusions: MCA provision increased over the first 5 years of the program; however, the number of persons receiving multiple MCAs is low. Initial recipients had a higher prevalence of disease, and greater medication use and costs compared with later recipients. MCAs were more frequently provided to Ontarians with a high burden of comorbid illness during initial years of service.

154. Pharmaceutical Opinions in Ontario: A Descriptive Analysis Using Administrative Claims Data

Lisa Dolovich,[1,2] Giulia P. Consiglio,[2] Elizabeth A. Bojarski,[2] Andrew J. Calzavara,[3] Linda D.

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MacKeigan,[2] Nedzad Pojskic,[4] Lori MacCallum,[5] and Suzanne M. Cadarette.[2,3] *[1]Department of Family Medicine, McMaster University, Hamilton, Canada; [2]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada; [3]Institute for Clinical Evaluative Sciences, Toronto, Canada; [4]Ontario Pharmacists Association, Toronto, Canada; [5]Banting and Best Diabetes Centre, University of Toronto, Toronto, Canada.*

Background: A pharmaceutical opinion (PO) is a community pharmacy service reimbursed since 2011 by the Ontario Drug Benefit (ODB) plan. It consists of a pharmacist's drug therapy recommendation to the prescriber with an outcome of the prescription being dispensed as prescribed, not dispensed or adjusted. The only provincial drug programs in Canada which reimburse for POs are Ontario and Quebec. Internationally, few similar programs could be found and were limited to Canada and the USA.

Objectives: The aim of this study was to describe the demographic and clinical characteristics of patients for whom a PO was rendered over a 2-year period in Ontario, Canada.

Methods: This cohort study leveraged linked administrative claims data from 1 April 2011 to 31 March 2013, including the ODB Program database. Descriptive statistics were calculated for PO recipients and stratified by age and sex. Trends over time were examined by plotting the number of services and unique PO recipients by type and month.

Results: The PO service was provided to 226 971 Ontarians from 1 April 2011 to 31 March 2013. Provision of POs more than doubled over these 2 years of the program, with dips in service levels during the summer. The majority of POs resulted in a recommendation to change a prescription (73%; similar across sexes). Over the 2 years of the program, 58% of recipients were women and 30% of recipients were social assistance beneficiaries (less than 66 years of age), consistent with the proportion of ODB social assistance recipients in Ontario. In the 30 days prior to a PO claim, 15% of all recipients had experienced a hospitalization or emergency department visit. In the year prior to a PO claim of those over 66 years of age, 12% had high medication costs ($4000+) and received an average of 11 prescription drugs. Only 27% of POs claims had a prescription filled on the same day.

Conclusions: The majority of PO recipients were seniors and women, similar to what we see for prescription volume. Most POs involved a recommendation to change the prescription. Most POs were not billed on the same day as the claimant's dispensed prescriptions, limiting our ability to identify the medication associated with each PO.

155. Predictors of Ontario's Medication Review Program (MedsCheck Annual Service) Utilization Among Ontario Seniors

Petros Pechlivanoglou,[1,2] Lusine Abrahamyan,[1,2] Linda MacKeigan,[2] Lisa Dolovich,[2,3] Giulia P. Consiglio,[2] Valeria E. Rac,[1,2] Jiandong Shin,[4] Paul Grootendorst,[2] Elizabeth A. Bojarski,[2] Suzanne M. Cadarette,[2,4] and Murray Krahn.[1,2,4] *[1]Toronto Health Economics and Technology Assessment Collaborative, University of Toronto, Toronto, ON, Canada; [2]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [3]Department of Family Medicine, McMaster University, Hamilton, ON, Canada; [4]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada.*

Background: A MedsCheck Annual (MCA) consultation is a government-funded, medication review service in Ontario, Canada, for people taking three or more prescription medications for chronic conditions.

Objectives: This study aimed to identify patient, pharmacy and community factors associated with the likelihood of Ontario seniors receiving MCA services between April 2012 and March 2013.

Methods: A conceptual framework was developed from published studies and the Ontario MedsCheck Guidebook that identified potential patient (e.g. demographics, clinical and medication information), pharmacy and community-level predictors (e.g. rurality and socioeconomic status) of MCA utilization. Using a random 20% sample from linked administrative datasets, we identified 'service dates' when a patient was eligible to receive an MCA. A mixed-effects logistic regression model was constructed using odds ratios (OR) to estimate the effect of each predictor on the likelihood of receiving MCA.

Results: We identified 65 605 MCAs provided during 2 878 958 eligible service dates. Compared with patients who did not receive an MCA, recipients of MCAs were more likely to be male (OR: 1.07), younger (OR: 1.02) and with fewer comorbidities (OR: 1.01) and medications (OR: 1.1) and were more

likely to have received a prior MCA (OR: 3.05). MCA recipients also had fewer hospitalizations and physician visits in the previous year (OR: 1.01), were recently discharged from hospital (OR: 1.08), were prescribed medications from a new drug class (OR: 1.96) or medications that were considered high risk (OR: 1.09) and were more adherent to cardiovascular medications (OR: 1.06). Individuals were less likely to receive an MCA if they were prescribed inappropriate medications (OR: 0.866), were living in a rural setting (OR: 0.76) or were visiting a high-volume pharmacy (OR: 0.610).

Conclusions: Of the patients that the program identified as most likely to benefit from MCAs, those prescribed a new or a high-risk drug or were recently hospitalized were more likely to obtain an MCA. Conversely, non-adherent patients with multiple comorbidities and medications were less likely to receive an MCA.

156. Incidence of Medication Errors in the Peri-operative Period: A Retrospective Study

Sarah Khayyat,[1] Sara Qureshi,[2] Li Wei.[3] *[1]Department of Clinical Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia; [2]Department of Pharmacy, St George's Healthcare NHS Trust, London, UK; [3]Department of Practice and Policy, UCL School of Pharmacy, London, UK.*

Background: Patients who undergo surgery will be at high risk of experiencing medication errors. One of the leading factors is the transferring of patients between different health providers, organisations and departments.

Objectives: The aim of this study was to identify the incidence of medication errors, types of errors and their location during the peri-operative period, in addition to identifying the common medications involved in these errors and finding recommendations to overcome it.

Methods: This was a retrospective study design conducted in two parts. The first part considered all medication error incidents through Datix reporting system from all theatres in a teaching hospital in London, UK. The second part reviewed medications of patients who were transferred to two emergency theatres within the hospital. Patient medications were reviewed over 24 hours before the surgery, during and 24 hours after the surgery for 3 days per week for 1 month. This established the incidence of medication errors and common drugs involved in these errors during the patients' peri-operative journey.

Results: In the first part of the study, 17 errors were identified. The total error rate was equal in both the pre-operative and post-operative period (29.4%) while it was high in the intra-operative period (41.2%). In the second part, the total number of errors identified was 407. Incidence in the intra-operative period was also high (59%), followed by the post-operative period (24.5%), pre-operative period in different hospital wards (14.5%) and pre-operative period in the accident and emergency department (2%).

Conclusions: This audit identified a significant number of medication errors in the peri-operative period. Demonstrating the contributing factors behind the incidence of these errors can assist in establishing recommendations to improve the hospital practice and ensure patient safety.

157. Hypothyroidism and Thyroid Hormone Use in Older Adults in Lazio, Italy

Ursula Kirchmayer,[1] Flavia Mayer,[1] Raffaele Antonelli Incalzi,[2] Mario Barbagallo,[3] Giuseppe Paolisso,[4] Gianpaolo Ceda,[5] Marina Davoli.[1] *[1]Department of Epidemiology, Lazio Regional Health Service, Rome, Lazio, Italy; [2]Department of Geriatric Medicine, Campus University Rome, Rome, Lazio, Italy; [3]Department of Internal Medicine and Specialties, University of Palermo, Palermo, Sicily, Italy; [4]Department of Internal Medicine, Surgical, Neurological, Metabolic Disease and Geriatric Medicine, Second University of Naples, Naples, Italy; [5]Geriatric Clinic, University Hospital of Parma, Parma, Emilia Romagna, Italy.*

Background: The prevalence of hypothyroidism increases with age and peaks in older women. Hypothyroidism in the elderly may be concealed by variant presentations and confounding by comorbidity. Thus, an important prevalence of unrecognized disease has been reported.

Objectives: This ecological study aimed to verify whether the consumption of thyroid hormones increases with age as expected on the basis of the epidemiology of hypothyroidism.

Methods: Design: A cross-sectional population-based study was performed using information from the regional health information systems. Setting: The study

refers to the Lazio region, Italy, with 5 million residents and more than 2.3 million residents aged 50 years and over. Participants: Residents aged 50+ years and registered in the regional health care system on 31 December 2012 were enrolled. Measurements: Use of thyroid hormones, comprising levothyroxine sodium, liothyronine sodium and their combinations, was defined as at least one prescription during 2012.

Results: Thyroid hormone users were 225 024 (9.4% of the study population), with more than 80% being women. The prevalence of thyroid hormone use progressively increased from the 50–54-year-olds (7.4%) to the 70–74-year-olds (12%) and then declined sharply to 7.4% in the 85–89-year-olds and 5.8% in the 90–94-year-olds. The cumulative yearly consumption was consistent with the yearly needs. Most users were burdened with important comorbidities and about two-thirds assumed six or more drugs.

Conclusions: Our findings suggest that hypothyroidism frequently remains unrecognized or untreated after the age of 75 years. Efforts should be made to confirm this finding and, then, to identify cost/effective screening strategies, at least for high risk elderly populations such as that with multimorbidity and frailty.

158. Prevalence and risk factors for adverse drug reactions in older adults in the acute care setting

Tariq M Alhawassi,[1,2] Ines Krass,[2] Lisa G Pont.[3] *[1]Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia [3]Sydney Nursing School, The University of Sydney, Sydney, New South Wales, Australia*

Background: Adverse drug reactions (ADRs) are common drug-related problems associated with increased morbidity, mortality and total healthcare costs in the general population, yet less is known about ADRs in older populations.

Objectives: The aims of this study were to estimate the prevalence of ADRs and identify factors associated with an increased ADR risk in an older population.

Methods: A retrospective cross-sectional survey of medical records at a large teaching hospital in metropolitan Sydney, Australia, was conducted. A systematic sample of all patients aged ≥65 years who were admitted between 1 January 2010 and 31 December 2010 was included. ADRs, defined according to the WHO definition, were identified by a trained clinical pharmacist. Causality was determined according to the Naranjo criteria and severity, preventability and contribution to hospitalisation by the Hallas criteria. Factors associated with an increased ADR risk were identified using multifactorial logistic regression.

Results: The study cohort comprised 503 patients (mean age (±SD) = 80.3 ± 8.2). Approximately one quarter of the cohort (26.2%) experienced an ADR. The majority of ADRs were classified as definite (4.5%) or probable (76.5%) and were considered the 'dominant' or 'partial' reason for admission in 20.5% and 12.1% of admissions, respectively. Approximately one-third (31.8%) of ADRs were considered severe and 47.6% moderate. Most were considered either definitely (15.2%) or possibly (50.0%) avoidable. Female gender (OR = 0.5, 95%CI [0.30, 0.80]), increased number of medications prior to admission (OR = 1.1, [1.03, 1.16]), previous allergy or ADR (OR = 4.9, [2.87, 8.40]), impaired renal function (OR = 0.9, [0.97, 0.99]) and current or past diagnosis of atrial fibrillation (OR = 2.0, [1.17, 3.28]) were all associated with an increased ADR risk.

Conclusions: ADRs are a considerable health problem for older persons. One quarter of all older persons admitted to hospital experienced an ADR, with three-fourth of these leading to serious outcomes. Of greater importance, 65% of all ADRs experienced by older persons were considered avoidable. Strategies to improve detection of ADRs and a greater awareness of those older persons at increased risk of an ADR are needed.

159. Adherence to evidence-based pharmacological therapies in patients with COPD: a multilevel analysis of patient, general practitioner and hospital of discharge

Martina Ventura, Mirko Di Martino, Danilo Fusco, Nera Agabiti, Giovanna Cappai, Marina Davoli. *Department of Epidemiology, Regional Health Service, Rome, Lazio, Italy*

Background: Guidelines for the management of chronic obstructive pulmonary disease (COPD) recommend regular treatment with long-acting bronchodilators (LB). However, observational studies reported poor adherence to evidence-based (EB) therapy.

Objectives: The objectives of the study were to describe drug-use patterns and to quantify how much of the 'distance from guidelines' is attributable to the patient, to the general practitioner (GP) or to the therapeutic approach given at hospital discharge.

Methods: Using linked health information systems of the Lazio region, we identified a cohort of patients discharged from hospital with a diagnosis of COPD between 2007 and 2011. Patients were followed up for 2 years, starting from the day of discharge. Adherence to guidelines was analyzed both in terms of 'continuity' and 'coverage' of EB therapy. Continuity was defined as at least one LB prescription in each 6-month period; adequate treatment coverage was defined as a medication possession ratio ≥80%. A cross-classified model was used to assess the variability in adherence attributable to the patient, GP and hospital of discharge and to identify the determinants of an adequate coverage.

Results: Among the 13 368 patients enrolled (males: 54.5%; mean age: 74 years), 37.6% were continuously treated with LB, and 29.9% were adequately covered by treatment. After controlling for socio-demographics and clinical conditions, adherence significantly varied among hospitals (variance = 0.097; $p < 0.0001$) and across GPs (variance = 0.044; $p = 0.091$). Respiratory conditions and proxies of COPD severity were associated with higher adherence. GPs working in group (OR = 1.11; 95%CI [0.99, 1.23]), teaching hospitals (OR = 1.33; 95%CI [1.02, 1.72]) and pneumology wards of discharge (OR = 1.26; 95%CI [1.06, 1.49]) were positively associated with adherence to EB therapy.

Conclusions: COPD pharmacotherapy is characterized by poor adherence to guidelines. A relevant proportion of variability is attributable to GPs and, above all, to the therapeutic approach recommended at hospital. The study results may be helpful to define priority areas for intervention in both primary care and hospital setting.

160. Clinical provider experiences with medication discontinuation

Amy Linsky,[1,2] Steven R Simon,[1,3] Kelly Stolzmann,[1] Mark Meterko.[1,4] *[1]VA Boston Healthcare System, Boston, MA, USA [2]Boston University School of Medicine, Boston, MA, USA [3]Brigham and Women's Hospital, Boston, MA, USA [4]Boston University School of Public Health, Boston, MA, USA*

Background: Medication adherence and reconciliation receive considerable attention, but there is less focus on improving intentional, proactive discontinuation of medications that may no longer be necessary.

Objectives: We developed and administered a nationwide survey of US Veterans Affairs (VA) primary care providers (PCPs) to assess attitudes toward and experiences with discontinuing medications.

Methods: We sampled 2475 VA clinicians with prescribing privileges [physicians, nurse practitioners (NPs), physicians' assistants (PAs), and clinical pharmacists]. Providers were asked about their experience and comfort with recommending medication discontinuation and their opinions of factors related to such decisions. We examined bivariate associations between clinician demographics and medication-relevant attitudes. We used backward elimination linear regression to build a multivariable model associating PCP factors with discontinuation recommendation.

Results: A total of 409 (17%) clinicians responded: 73% physicians, 17% NP/PAs, and 10% pharmacists. Participants were mostly White (72%), female (52%), and aged >50 years (64%); had ≥8 clinic sessions/week (52%); had worked in VA <10 years (53%); and had prior experience working outside VA (79%). Overall, 38% of respondents reported that >40% of their patients had a medication that could potentially be stopped, and 78% indicated that >20% of their patients had potential discontinuation. However, among the PCPs who identified such patients, 11% recommended discontinuation to <20% of candidate patients, while only 30% recommended discontinuation for >80% of candidates. In multivariable analyses, factors associated with recommending discontinuation included self-rated comfort level with medication discontinuation ($p < 0.0001$) and prior non-VA clinical experience ($p = 0.048$).

Conclusions: Nearly all clinicians had patients with medications that could potentially be stopped, yet whether they actually made a recommendation to do so varied. Given that self-rated comfort with discontinuation and practice experience were associated with taking action, it is essential to understand the factors contributing to comfort level so as to develop interventions leading to safer prescribing.

161. Non-compliance with guideline on NSAID use and gastroprotection in hospitalized surgical patients who are prescribed NSAIDs

Naoual Chaaouit,[1] Michael HJ Verhofstad,[2] Esther MM van Lieshout,[2] Patricia MLA van den Bemt.[3]
[1]Utrecht University, Utrecht, The Netherlands [2]Department of Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands [3]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands

Background: Since nonsteroidal anti-inflammatory drugs (NSAIDs) can cause serious upper gastrointestinal (GI) harm, clinical guidelines have been established for the prescribing of proton pump inhibitors (PPIs) in high-risk patients. Several studies have shown that these guidelines are often not complied with. However, these settings generally do not include hospitalized patients. Yet, potential consequences of non-compliance may be serious in this specific population.

Objectives: The objectives of this study were to assess the proportion of non-compliance with the Dutch guideline on NSAID use and gastroprotection and to determine the association of several factors with guideline non-compliance.

Methods: Study design: A single-centre, retrospective database study.

Study population: Hospital admissions on surgical wards of the Erasmus University Medical Center between 1 January 2013 and 1 August 2014 in which an NSAID was newly prescribed. Excluded was preadmission PPI use.

Main outcome: Proportion of non-compliance with the guideline. Secondary outcome: the association of several factors with non-compliance.

Data analysis: The proportion of guideline non-compliance was calculated as the percentage of all included hospital admissions. For the secondary analysis, univariate and multivariate logistic regression analysis was performed.

Results: Four-hundred eighty hospital admissions were screened, of which 249 admissions were included. Main reason for exclusion was the use of NSAID and/or PPI before hospitalization. The proportion of hospital admissions in which guideline non-compliance was present was 46.6%, mostly due to incorrectly added PPIs. Coxib use (adjusted OR 0.22; 95% confidence interval [0.11, 0.43]), polypharmacy defined as the use of five or more drugs (2.18; [1.27, 3.76]) and the surgical wards orthopedics (22.32; [5.38,92.55]), plastic surgery (10.82; [2.51, 46.59]), trauma surgery (5.78; [1.47, 22.70]) and transplant/vascular surgery (4.45; [1.10, 18.00]) were statistically significantly associated with non-compliance.

Conclusions: Non-compliance with the guideline on NSAID use and gastroprotection is present in almost half of surgical hospital admissions and mainly concerns overprescribing.

162. Hypertension management and control in older persons on admission to an acute care setting

Tariq M Alhawassi,[1,2] Ines Krass,[1] Lisa G Pont.[3]
[1]Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia [2]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia [3]Sydney Nursing School, The University of Sydney, Sydney, New South Wales, Australia

Background: Despite good evidence that managing hypertension in older adults reduces mortality and morbidity, there are limited data regarding current practices in the management of hypertension in older people.

Objectives: The aims of this study were to explore the management of hypertension in older people and to identify factors associated with sub-optimal blood pressure (BP) control in older population.

Methods: A retrospective cross-sectional study of 503 patients aged ≥65 years admitted to a large metropolitan teaching hospital in New South Wales, Australia, was conducted. The main outcome measures were BP control and antihypertensive medication use. Patients were considered to be at target BP control if they met the current national guideline for the management of hypertension. A block entry logistic regression model was used, and all factors significant in the univariate analysis were included in one step in the multivariate model. Statistical significance was considered at a probability value of <0.05.

Results: Sixty-nine percent ($n = 347$) of the study population had a documented diagnosis of hypertension. Of these, 54.5% were at target BP levels on admission

to hospital. The median number (±IQR) of antihypertensive agents per patient was 2.0 (1.0–2.0). Angiotensin II receptor blockers were the most commonly used medication type, followed closely by ACEI and CCB. Male gender (OR = 1.71, 1.07–2.74), increasing number of antihypertensive medications (OR = 1.95, 1.15–3.32) and past history of a myocardial infarction (OR = 1.28, 1.03–1.60) were all associated with better BP control in older population with hypertension.

Conclusions: In conclusion, while older hypertension patients are receiving antihypertensive pharmacotherapy, many older adult patients do not have optimal hypertension control and are not reaching target BP levels. Multidisciplinary healthcare services including clinical pharmacists may potentially improve hypertension management and antihypertensive medication prescription in older persons with hypertension.

163. Study of drug utilization pattern of antidiabetic agents: analysis on the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

Roberta Carvalho de Figueiredo, Thaís Resende Batista, Raiany Thaimeny Nery. *Mid-West Campus, Federal University of São João del-Rei, Divinópolis, Minas Gerais, Brazil*

Background: Studies conducted in Brazil have demonstrated that most of the direct cost associated to diabetes is attributed to medication; however, little is known about the Brazilians' pattern of antihyperglycemic agents use.

Objectives: The aim of this study was to characterize the pattern of oral hypoglycemic agents and insulin use among the baseline participants of the Longitudinal Study of Adult Health (ELSA-Brasil) according to sociodemographic factors, diabetes duration and glycemic control estimated by glycated haemoglobin (HbAlc).

Methods: This analysis included 1520 participants with diabetes (self-reported clinical diagnosis of diabetes and/or use of medication for diabetes control) from the ELSA-Brasil baseline, a cohort that investigates incidence and predictors of chronic diseases among 15 105 civil servants from six public educational institutions located in different regions of Brazil. Differences between proportions were estimated using the chi-square test.

Results: Monotherapy was the most widely used treatment regimen; 48.8% of the participants were using only one oral hypoglycemic, and only 4.7% of them had used insulin alone. In relation to oral hypoglycemic agents, metformin was the most used (41.8%). The use of monotherapy was more frequent among subjects with less time of diabetes diagnosis and adequate HbA1c levels (<7%). Among older subjects (≥60 years) with HbA1C inadequate levels, the most common regimen was the combination of metformin and insulin. Additionally, besides the antidiabetic agents, on average, the participants had used 3.2 (SD = 2.7) drugs, mainly those for the cardiovascular system and nervous system.

Conclusions: Drug utilization studies in the ELSA-Brasil take a step forward in pharmacoepidemiological research of diabetes in Brazil. The information constructed by the drug utilization studies could be the beginning of the desired change in the professional practices, contributing to the rational use of drugs, and could contribute substantially to the development of preventive programmes and the formulation of public policies to reduce the impact of the disease.

164. Results of the European Science Foundation exploratory workshop on quality and safety of pharmacotherapy in old age: a focus on potentially inappropriate medication (PIM) lists

Majda Azermai, Monique Elseviers, Robert Vander Stichele, On Behalf of the European Science Foundation Exploratory Workshop Members. *Heymans Institute of Pharmacology, Gent, Belgium*

Background: On 12–14 June 2014, international experts gathered in Ghent, Belgium, for a European Science Foundation workshop focusing on pharmacotherapy in old age.

Objectives: The aim was to define the requirements for electronic assessment of potentially inappropriate medication (PIM) lists.

Methods: A total of 15 experts gathered from eight European countries. Five sessions were organized on the different aspects of evaluating quality and safety (conceptual framework, inventory of existing PIM lists and PIMs suitable for electronic assessment, limitations of applications of electronic PIMs, relationship with quality indicators and future perspectives). The

results of the five sessions were translated by the scientific committee into draft recommendations, which were then discussed by the experts to establish consensus for the final recommendations.

Results: The members formulated recommendations on 11 domains regarding quality of pharmacotherapy. The following recommendations were formulated regarding PIM lists: the focus should be on existing European lists including START/STOPP, PRISCUS, LAROCHE and NORGEP. It is not needed to engage in the process of creating a new European list. However, an inventory should be maintained of existing lists, which have undergone efforts of validation of their contents, with identification of PIMs suitable for electronic, broad and regular evaluation of pharmacotherapy and with the distinction between drug-oriented and more clinically oriented PIMs. Prerequisites for electronic assessment involve precise codification of medication, clinical data and the decision rules to permit international secondary use of routinely collected clinical data. Throughout the development cycle of PIMs, the suitability for electronic application should be considered.

Conclusions: The requirements for the electronic use of PIMs for the regular screening of the quality of pharmacotherapy in old age are rarely fulfilled and only available at the national level in a few countries. Before a more generalized international utilization can be promoted, work has to be done at a European level.

165. Evaluation of a rapid implementation quality improvement programme for medicine security

Alice V Gilbert,[1,2] Michael Roberts,[2,3] Des Williams,[3] Andrew Leigh Gilbert.[3] *[1]Pharmacy, Top End Health Service, Darwin, Northern Territory, Australia [2]School of Medicine, University of Queensland, Brisbane, Queensland, Australia [3]Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia*

Background: Certain Schedule 4 (prescription only) medicines are subject to further restriction of supply, distribution and possession, to reduce abuse, misuse and physical/psychological dependence. In Australia, these medicines are restricted schedule 4's (S4R's). Mental health (MH) is recognised as high risk for medication misadventure. The management of S4R's within MH at the study hospital was poor, and rapid change was required to prevent harm. The management of S4R's did not comply with the policy or the best practice.

Objectives: The objectives were to implement and evaluate a rapid change management programme to transition S4R medicines in line with the best practice and the policy.

Methods: Baseline evaluation of S4R medicines was completed using pre- and post-supply data from dispensing software. A communication strategy was implemented in order to communicate this project internally; strategies included text message notification, education sessions and training handbooks. This change was implemented within 48 hours. Feedback was sort from nursing staff, and an audit was conducted to review practice against policy.

Results: Zero percent of S4R's were being stored and managed in line with the policy at baseline; 100% are now stored correctly. Supply reports for the five most common S4R's all decreased post-implementation; diazepam 5-mg tablets decreased by 993 (41%), temazepam 10-mg tablets by 325 (76%), paracetamol/codeine 500/30-mg tablets by 120 (40%), lorazepam 1-mg tablets by 25 (10%) and midazolam 5-mg/mL ampules 35 (58% reduction). Seventy-five percent (9 out of 12) of nursing staff were satisfied with the information provided. Ninety-two percent (11 out of 12) received information with the highest proportion (73%) via email. Eighty-three percent had been provided with the knowledge and skills required to manage this new system, and 63% (7 out of 12) do not require additional information. Fifteen indicators were audited against 920 entries in the S4R register to assess policy compliance. Six indicators showed 100% compliance, e.g. signed by second nurse, balance completed three shifts/day. The remaining showed good compliance, e.g. date noted (99%) and prescribers name (94%).

Conclusions: Rapid implementation for the best practice management of S4R's has demonstrated high uptake of policy and a decrease in supply.

166. A multinational, drug utilisation study to investigate the use of dexmedetomidine (Dexdor®) in clinical practice in the EU

Susana Perez-Gutthann,[1] Mary Weatherall,[2] Chris Garratt,[2] Pasi Pohjanjousi,[3] Riku Aantaa,[4] Giorgio Conti,[5] Michael Lewis,[6] Nicholas Moore.[7] *[1]RTI Health Solutions, Barcelona, Spain [2]Clinical*

Development, Orion Pharma, Nottingham, UK [3]Biostatistics, Orion Pharma, Kuopio, Finland [4]Perioperative Services, Intensive Care, Emergency Care and Pain Medicine, University of Turku, Turku, Finland [5]Anaesthesia and Intensive Care Medicine, Catholic University of Rome, Rome, Italy [6]EPES Epidemiology GmbH, Berlin, Germany [7]Bordeaux Pharmacoepi, University of Bordeaux, Bordeaux, France

Background: Dexmedetomidine (Dex) is a sedative drug approved as Dexdor® for ICU sedation in adults in the European Union in 2011. This observational, retrospective drug utilisation study was requested by the Committee for Human Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to investigate Dex use in clinical practice.

Objectives: The objective of the study was to evaluate how Dex is used in the EU, with particular focus on off-label use including the paediatric population.

Methods: Study countries and sites were chosen from those with highest dexdor use, based on sales. Site selection (blind) was conducted by a multinational, multi-specialist, independent group. All patients treated with Dex at the study sites during the enrolment period were to be included. Anonymised data on demographics, treatment indication, Dex dosing, concomitant medications and treatment effectiveness were collected retrospectively from the patient records. Informed consent was waived to avoid influence of the study on the prescribing of Dex. Recruitment was limited to 750 patients per country or 300 patients per study site and was completed within 18 months of the first site initiation.

Results: Data from 2000 patients were collected from 16 hospitals in four EU countries (Finland 750, Poland 505, Germany 470 and Austria 275) between 13th June 2013 and 4th December 2014. The median age was 62 years, with more males (70.2%) than females. The overall proportion of paediatric patients was 5.2% with the highest incidence in Austria and Finland. Dex was primarily used in adult ICU (86.0%) for ICU sedation (78.6%) and mostly dosed according to the product label. Overall, in 84.9% of administrations, the intended sedative effect was obtained.

Conclusions: This drug utilisation study indicates that dexmedetomidine (Dexdor®) is mostly used according to the terms of its product licence in the EU, although a variable degree of use was also seen in other settings and populations.

167. An academic detailing program to reduce antipsychotic medication use in nursing homes

Eimir Hurley,[1,2] Connie DiCocco,[2] Michael Fischer,[1,2] Niteesh Choudhry,[1,2] Jerry Avorn.[1,2] *[1]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA, USA [2]Alosa Foundation, Boston, MA, USA*

Background: The use of antipsychotic medications (APMs) in patients with dementia has been associated with a 60–70% increase in risk of death and carries an FDA black box warning. Despite this, more than 20% of nursing home residents in the US receive these medications. Academic detailing (AD) is a program of proactive educational outreach of evidence-based prescribing guidance that has been shown to improve medication use.

Objectives: Targeting nursing homes with higher rates of APM use, we implemented a state-wide AD intervention that presented evidence-based alternatives to antipsychotic medications for managing patients with dementia, targeting clinicians and other staff.

Methods: Adopting a quasi-experimental, stepped wedge approach, we designated groups of facilities to receive the intensive intervention each quarter. Staff members were surveyed regarding the program while waiting for accrual of data on changes in medication use.

Results: Between May and December 2014, the intervention was fully completed in 95 facilities, with 677 staff receiving at least one educational session with a trained academic detailer (median staff educated per facility, 6; range, 3–30). Of the 528 survey respondents, 75% strongly agreed that they would review the use of antipsychotic medications and taper and withdraw unless clinically indicated. At baseline, 8.0–57.1% of residents in participating homes received an antipsychotic in the quarter immediately preceding the intervention. Analysis of the impact of the intervention on APM use will utilize the data available mid-2015.

Conclusions: Despite pressure from multiple sources to reduce the use of APMs in vulnerable nursing home patients, wide variation exists in their use. We have successfully implemented an academic detailing program to educate clinicians and other

staffon evidence-based alternatives to APMs, including non-drug options. Subjects received the intervention positively; forthcoming APM utilization data will determine whether prescribing behavior changed.

168. Availability of essential medicines for children in Armenia

Irina Kazaryan,[1] Lusine Vardanyan.[2] *[1]Drug Utilization Research Group PO, Yerevan, Armenia [2]Pharmaceutical Management, Yerevan State Medical University, Yerevan, Armenia*

Background: There is a lack of medicines in special formulations intended for children. Even if medicines exist in such dosage forms, they are often not available in low- and middle-income countries.

Objectives: The objective of this work was to assess the situation with availability of essential medicines for children in Armenia.

Methods: The World Health Organization (WHO) 4th Model List of Essential Medicines for Children (EMLc) was compared with the List of medicines registered in Armenia (2013). The price lists of main local wholesalers were analyzed. In 2013, availability of 37 key tracer paediatric medicines was studied in 33 community pharmacies from all the regions of Armenia. Methodology recommended by WHO (Better Medicines for Children project) was used.

Results: The percent of medicines from WHO EMLc, which were registered in Armenia in 2013, is 31.9%. The percent of pharmaceuticals from the WHO EMLc (without taking into account dosage forms and doses) distributed by main wholesalers is 56.1%. Only 13 of 37 key medicines were available at community pharmacies; they were from five of 10 therapeutic groups selected for the study. Sixteen of 24 missing medicines were available in formulations and dose others than those selected for the study. Amoxicillin/clavulanic acid suspension, 125 mg + 31.25 mg/5 ml, was not available at any pharmacy studied despite the fact that this medicine is on the Armenian Essential Medicines List (AEML) and it is authorized and included in approved clinical guidelines for children. Only three of 13 studied medicines available on the pharmaceutical market were found out in all 33 pharmacies: ibuprofen (tablets, 200 mg), dexamethasone (eye drops, 0.1%) and xylometazoline (nasal spray, 0.05%). The situation on availability of medicines within each of the five groups observed in Yerevan and other regions was similar.

Conclusions: Many essential medicines for children are not authorized in Armenia and not available at community pharmacies; that means a lack of access to efficacious, safe and cost-effective medicines for this vulnerable group of patients. There is an urgent need for introducing efficient measures addressing this situation. The first step suggested is the approval of the AEML for children.

169. Real-world analysis of taxane use in the first-line setting and prior comorbidities among female metastatic triple-negative breast cancer patients

Shih-Wen Lin,[1] Dixa Thakrar,[2] Joseph Simpson,[1] Roel Funke,[1] Stephen Chui.[1] *[1]Genentech Inc., South San Francisco, CA, USA [2]School of Medicine, University of Leicester, Leicester, UK*

Background: There are no standard approaches for selecting ≥1-L chemotherapy for metastatic triple-negative breast cancer (TNBC). Taxanes have an increasingly important role in breast cancer treatment; however, their real-world use in TNBC is not well described.

Objectives: Using a large US insurance claims database, we assessed the use of taxanes in metastatic TNBC patients in the 1-L setting and characterized patient comorbidities by taxane use.

Methods: A retrospective analysis of the MarketScan Commercial Claims and Medicare data was conducted to assess the patterns of taxane use among female metastatic TNBC patient diagnosed between 1 January 2005 and 30 June 2013. These patients were identified if they had ICD-9-CM codes for primary breast cancer and metastases, administrative claims for a HER2 test and did not receive hormonal therapies or anti-HER2 therapy. The use of 1 L taxanes (paclitaxel, docetaxel and nab-paclitaxel) was defined by administrative claims within 6 months after initial metastatic diagnosis, and pt comorbidities were identified during the 12 months prior to diagnosis.

Results: Among the 10 750 TNBC patients (mean age 57.4 years) identified, 4946 (46%) received a taxane in the 1 L setting, either as a single agent or in

combination therapy. Most taxane users (95.6%) had not received any taxanes prior to initial diagnosis. Among those receiving 1-L taxanes (mean age 54.3 years), the majority received paclitaxel (54.5%), followed by docetaxel (39.1%) and nab-paclitaxel (6.4%). Several comorbidities were significantly ($p < 0.05$; unadjusted) less common among those receiving taxane regimens vs those receiving non-taxane regimens, including cardiac failure, chronic obstructive pulmonary disease, chronic bronchitis, liver disorders, gastritis, venous embolism and lymphoma.

Conclusions: In this real-world data analysis, nearly half of metastatic TNBC patients received 1-L taxane-containing regimens. Those receiving taxanes were less likely to have comorbidities and less likely to have previously received adjuvant taxane vs those who received non-taxane regimens, suggesting that comorbidities and prior treatment may influence TNBC treatment.

170. Withdrawn by author

171. Questionable care: use of memantine hydrochloride and cholinesterase inhibitors in patients with advanced dementia at the end of life who were enrolled in a hospice

Jacob N. Hunnicutt, Jennifer Tjia, Kate L. Lapane. *Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA*

Background: The Food and Drug Administration approved memantine hydrochloride and cholinesterase inhibitors for the treatment of moderate to severe dementia. For those with advanced dementia (severe cognitive impairment and functional dependency) receiving hospice care, the benefit of such medications is questionable.

Objectives: The objectives were as follows: (1) to estimate the prevalence of memantine hydrochloride and cholinesterase inhibitors in patients with dementia on a hospice and (2) to examine the characteristics associated with the use of either medication.

Methods: We conducted a cross-sectional study using data from the 2007 National Home and Hospice Care Survey, a nationally representative sample of U.S. hospice agencies. We identified 439 patients diagnosed with dementia at admission, ≥65 years of age, discharged from a hospice with medication records (representing 108 368 U.S. adults). Use of up to 25 medications used in the 7 days before death was documented. Logistic regression weighted to account for the complex sampling design provided estimates of the association between resident and facility characteristics and the use of either medication.

Results: In the 7 days before death, 13.2% (95% confidence interval (CI [7.96%, 18.45%]) used a cholinesterase inhibitor and/or memantine with 7.2% (95%CI [2.97%, 11.53%] using a cholinesterase inhibitor only, 3.7% (95%CI [1.14%, 6.28%]) using memantine only, and 6.0% (95%CI [2.36%, 9.66%]) using both medications. In adjusted analyses, gender, age, Medicaid insurance, tube feeding, DNR, location of hospice, length of stay, and profit orientation were not associated with use. Patients enrolled in hospice agencies in less populated areas had increased odds of receiving cholinesterase inhibitors and/or memantine (aOR: 2.64; 95%CI [1.21, 5.79]).

Conclusions: In patients with advanced dementia receiving palliative care, use of medications with questionable benefit is non-trivial. Research to further our understanding of how to maintain palliative care goals but reduce unnecessary medication use is warranted.

172. Withdrawn by author

173. Withdrawn by author

174. Withdrawn by author

175. Agreement between self-reported medication from patient questionnaires with physician information: results from a long-term cohort with coronary heart disease

Dietrich Rothenbacher,[1] Andrea Jaensch,[1] Ute Mons,[2] Lutz Breitling,[2] Dhayana Dallmeier,[3] Harry Hahmann,[4] Hermann Brenner.[2] *[1]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany [2]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany [3]Department of Internal Medicine II-Cardiology, Ulm Medical Center, Ulm, Germany [4]Klinik Schwabenland, Isny, Germany*

Background: In observational studies, information regarding medication is often collected via questionnaires from patients.

Objectives: The aims of this study were to evaluate the agreement between medication from patients' self-reports and information obtained from caring practitioners in a cohort of patients with coronary heart disease (CHD) and compare results during a long-term follow-up.

Methods: We conducted a prospective cohort study in CHD patients aged 30–70 years undergoing an inpatient rehabilitation programme. During a 10-year follow-up, prescription information was collected from patients via questionnaires and, in parallel, from caring physicians. Agreement between patients' response and physicians' information was assessed 1-, 3-, 4.5-, 6- and 10-year follow-up by calculation of kappa statistics with 95% confidence intervals.

Results: Overall, 1009 of 1206 patients with CHD were included (85% men, median age 61 years). During a follow-up, almost all prognostic relevant cardiovascular medications increased, whereas aspirin and nitrates decreased. Beta-blockers and statins showed almost no change during a follow-up. Few patients received psycholeptics or antidepressants (2.7% and 3.1%). There was a marginal difference between patients-reported prescriptions and physician-reported ones. The kappa coefficients indicated a good to very good agreement (i.e. 0.93, 0.86, 0.82, 0.88 and 0.81 for clopidogrel/ticlopidin or 0.92, 0.92, 0.93, 0.89 and 0.92 for calcium channel blockers during respective follow-up years). Insulin und pure ACE-blockers showed a lower, but partly, still good agreement (kappa between 0.65 and 0.84); oral antidiabetic medications showed also a good agreement. The lowest kappa was found for psycholeptics (0.50 during a 4.5-year follow-up) and for antidepressants (0.54 during 10-year follow-up). Results in elderly patients (>65 years) were only marginally different.

Conclusions: The results of this study showed a good to very good agreement between patient-reported medications and physician-reported ones for prescribed cardiovascular and antidiabetic medication in patients with CHD.

176. Concordance among anticholinergic burden scales

Jennifer G Naples,[1] Zachary A Marcum,[2] Subashan Perera,[1] Shelly L Gray,[2] Anne B Newman,[3] Eleanor M Simonsick,[4] Kristine Yaffe,[5] Ronald I Shorr,[6] Joseph T Hanlon.[1] *[1]Medicine (Geriatrics), University of Pittsburgh, Pittsburgh, PA, USA [2]Pharmacy, University of Washington, Seattle, WA, USA [3]Public Health (Epidemiology), University of Pittsburgh, Pittsburgh, PA, USA [4]Intramural Research Program, National Institute on Aging, Baltimore, MD, USA [5]Medicine and Psychiatry, University of California, San Francisco, San Francisco, CA, USA [6]GRECC, North Florida/South Georgia Veterans Health System, Gainesville, FL, USA*

Background: There is no gold standard to assess potential anticholinergic burden of medications.

Objectives: The aim of the study was to evaluate concordance among multiple anticholinergic scales.

Methods: Study design was a cross-sectional secondary analysis of self-reported baseline medication data for 3055 community-dwelling older adults aged 70–79 years from the Health, Aging, and Body Composition (Health ABC) study.

Setting: The study took place in Pittsburgh, PA, USA, and Memphis, TN, USA.

Main outcome measure: Any use, weighted scores (total scores 0, 1–2, >2) and summated standard daily dosage (participant daily dose divided by minimum effective dose then summed across agents) were calculated using five anticholinergic measures (Anticholinergic Drug Scale [ADS], Anticholinergic Cognitive Burden [ACB] Scale, Anticholinergic Risk Scale [ARS], Drug Burden Index anticholinergic component [DBI-ACh], and Summated Anticholinergic Medications Scale [SAMS]).

Statistical analysis: Concordance was evaluated with kappa statistics and Spearman rank correlations.

Results: Any anticholinergic use was 43% for the ADS, 51% for the ACB, 23% for the ARS, 29% for the DBI-ACh, and 16% for the SAMS. Pairwise kappa statistics ranged from 0.33 to 0.68. Similarly, weighted kappa statistics ranged from 0.54 to 0.70 among the three scales using weighted scores to create categorical variables (ADS, ARS, and ACB). Spearman rank correlation between the DBI-ACh and the SAMS-summated standard daily dosage was 0.50.

Conclusions: Only poor to moderate concordance was found among the five anticholinergic scales. Future

research is needed to examine how these differences in measurement impact their predictive validity with respect to clinically relevant outcomes, such as cognitive impairment.

177. An assessment of the basic medication safety practices in Sudan

Mansour A Mahmoud, Shihabeddin Siddig,[2] Alnada Mohamed, Hisham Aljadhey. *[1]Discipline of Social and Administrative Pharmacy, Universiti Sains Malaysia, Penang, Malaysia [2]Bashayer Teaching Hospital, Khartoum State Ministry of Health, Khartoum, Sudan [3]Head Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan [4]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*

Background: Medication safety is crucial to the quality of patient care and remains as a major challenge especially in developing countries. There is a widespread acknowledgement of the importance of establishing medication safety practices in healthcare organizations. As a result, assessing the current state of medication safety practices in healthcare organizations has become a common activity to improve patient safety.

Objectives: The aim was to assess the presence of medication safety practices in Khartoum State hospitals.

Methods: This study is a descriptive cross-sectional study.

Setting: The study took place at hospitals in Khartoum State, Sudan.

Study tool and data collection: We adopted a questionnaire on evaluating medication safety practices in hospitals from a previous study. A total of 41 senior pharmacists or pharmacy supervisors from 41 hospitals were interviewed. We collected information on demographic characteristics of the hospitals. The core practices evaluated were the presence of medication safety committee and error reporting system, Look-Alike Sound-Alike medications list, control of concentrated electrolyte solutions, care transitions, information technology, drug information and other medication safety practices.

Results: Forty-one hospitals were surveyed. Only 2.4% of the hospitals had a list of LASA medications, and 4.9% had a list of error-prone abbreviations. Only 4.9% of the hospitals had a medication safety committee, and none of the hospitals had a medication safety officer. None of the hospitals involved pharmacists to obtain medication histories, and 87.5% of the hospitals provided a medication list to the patients at discharge. Concentrated electrolytes were available in floor stock in 66.7% of the hospitals, whereas 24.4% of the hospitals used a computer system in their pharmacy to enter prescriptions and none of these hospitals required entry of patient's allergies before entering a drug order.

Conclusions: Majority of the hospitals in Khartoum State do not implement basics of medication safety practices. In Sudan, an effort must be made by the ministry of health to enforce laws and regulations that make the implementation of medication safety practices mandatory to ensure patient safety.

178. Applicability of a systematic tool to reduce inappropriate prescribing in adults with an intellectual disability: a pilot study

Rianne J Zaal,[1] Susan Ebbers,[2] Mirka Borms,[3] Bart de Koning,[4] Patricia MLA van den Bemt,[1] Heleen M Evenhuis.[5] *[1]Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands [2]DeSeizoenen, Oploo, Netherlands [3]Het Raamwerk, Noordwijkerhout, The Netherlands [4]Pluryn, Nijmegen, The Netherlands [5]Family Medicine, Erasmus MC, Rotterdam, The Netherlands*

Background: For older patients with polypharmacy in the general population, a Systematic Tool to Reduce Inappropriate Prescribing (STRIP) has been developed, based on START/STOPP criteria. Although annual medication review is recommended for people with an intellectual disability (ID), a specific tool for this population is not available.

Objectives: This pilot study was performed to evaluate the applicability of STRIP in adults with ID living in a centralized setting.

Methods: This pilot study was performed in three care organizations. In each organization, nine clients with polypharmacy (i.e. concomitant use of ≥5 drugs), their legal representatives and mentors were invited for a review using STRIP. The reviews were performed by the responsible pharmacists and the investigators (resident ID physicians). Primary outcome was the applicability according to the following criteria: (1) a client and/or his

legal representative were present during at least 80% of the reviews; (2) at least 80% of the mentors were involved in the medication review; (3) medication review identifies drug-related problems; (4) at least 67% of the interventions to resolve drug-related problems were implemented 6 months after the review; and (5) medication review results in net savings of medication costs, assuming that at least 67% of the interventions were implemented.

Results: The client and/or a legal representative were present during 25 of 27 reviews (93%), and all 27 mentors (100%) were involved (complies with criteria 1 and 2). In total, 127 drug-related problems were identified, and for each patient, at least one problem was detected (complies with criterion 3). Six months after review, 15.7% of the interventions were partially or completely implemented (does not comply with criterion 4). When the implementation grade would have been 67%, medication review would have resulted in net savings of medication costs of €20 636 (complies with criterion 5).

Conclusions: STRIP seems applicable to adults with an ID, but the implementation of suggested interventions was too low. To improve the implementation grade, the treating physician should be involved in the review process.

179. Medications prescribed and stopped at hospital discharge and filled medications in the community: medication discrepancies 30-day post-hospital discharge

Daniala L. Weir, Aude Motulsky, Maria-Teresa Moraga, Robyn Tamblyn. *McGill University, Montreal, Canada.*

Background: Hospitalization is associated with numerous changes in patient medication regimens. Currently, efforts are being made to improve medication reconciliation practices at the time of hospital admission and discharge to decrease the probability of unintended modifications.

Objectives: The aim of the study is to estimate medication discrepancies between hospital discharge prescriptions and filled medications 30 days after discharge, when an electronic medication reconciliation tool is used at the time of discharge.

Methods: We conducted a prospective cohort study of patients seen at McGill University Health Center in Montreal, Quebec, Canada, from May to December 2014. Medication discrepancies were evaluated within 30 days of discharge and were defined as community medications that were discontinued at discharge and subsequently filled in the community or medications that were prescribed at discharge and not filled in the community. Multilevel logistic regression was used to estimate predictors of discrepancies and account for patient-level clustering.

Results: Among the 254 individuals included in our cohort, mean age (SD) was 70 (15), 41% were female and 38% had 3+ chronic conditions. Patients were prescribed a total of 3096 medications at discharge (12 on average per person); 57% were continued community medications, and 43% were added during the hospital stay; 1223 (40%) were not filled in community, while of the 717 discontinued community medications, 12 (2%) were dispensed post-discharge. Of drugs not filled in the community, 41% were newly added medications, and 59% were continued from community. After removing drugs prescribed 'as needed' (such as adrenergic agonists, e.g. salbutamol), the proportion of discrepancies was 38%. Patient-level predictors of discrepancies included younger age (<80 years) and increasing patient complexity in terms of the number of drugs and chronic conditions.

Conclusions: Medication discrepancies post-discharged are common; thus, further research is required to develop more targeted interventions for prevention.

180. Completeness of medications prescriptions: prescription errors study in Hail Region (PeSHR)

Ali F. Altebenaui,[1] Mubarek Alrashedi,[1] Thamir M. Alshammari,[1,2] Mohamad Aljofan.[1] *[1]Clinical Pharmacy, University of Hail, Hail, Saudi Arabia [2]Medication Safety Research Chair, King Saud University, Riyadh, Saudi Arabia*

Background: Medication errors can occur during any of the medical treatment phases that begin with diagnosis and finishes with drug dispensing. Prescription errors are commonly occurring errors that can lead to multiple errors, potentially placing patient lives in jeopardy.

Objectives: The current study aims at identifying the types and frequency of prescription errors in a referral tertiary hospital in Hail city, the regions' largest hospital.

Methods: This study is a retrospective cross-sectional analysis of physician prescriptions that were issued over a 1-month period (October–November 2014). Researchers have randomly selected and reviewed 1000 written prescriptions from different departments (outpatients clinics and ER) for any potential errors as per Neville's classification. Prescription errors were classified as major (potentially life threatening), minor (non-life threatening) or trivial. Descriptive statistics were used to report responses using statistical analyses software (SAS 9.3). A chi-square test or Fisher exact tests were used to analyse the categorical data. All statistical tests were conducted with a two-tailed alpha of 0.05.

Results: While the majority of the reviewed prescriptions have at least one error, alarmingly 8 out of the 1000 reviewed prescriptions had no patient name or file number. Amongst other errors, patient file numbers and medication dosages were missing in more than 20% and 40%, respectively. At least 30% of the reviewed prescriptions were deemed to have had illegible handwriting, which requires pharmacist judgement to decipher the writing. Non-life threatening items including age, physician signature and stamp, date, sex diagnosis and weight were missing in more than 50%, with the latter missing from all transcripts. Prescriptions wrote by ER physicians had more missing items compared with those wrote by outpatients clinics ($p = 0.01$).

Conclusions: While avoidable errors will continue to occur for many different reasons, there is an urgent need for a system to force prescribers to write all prescription items. Further studies are required to assess other medication errors source in Hail city and all over Saudi Arabia.

181. Prevalence of potentially inappropriate medication prescribing among older adults in emergency department in Chile

Marcela Jirón,[1] Luis Herrada,[2] Alex Rojas,[1] Andrés Lueiza,[1] Elena Vega,[1] Erwin Buckel,[2] Hernán Acuña,[2] José Luis Santelices,[2] Renato Maynard,[2] Ricardo Quezada.[2] *[1]Ciencias y Tecnologia Farmaceutica, Facultad de Ciencias Quimicas y Farmaceuticas, University of Chile, Santiago, Chile [2]Urgencias, Clinica las Condes, Santiago, Chile*

Background: Potentially inappropriate medications (PIM) increase the risk of adverse effects of drugs in older adults. Prevalence of PIM in emergency department (ED) has been less explored.

Objectives: The objective of the study is to determine the prevalence of PIM among Chilean older adults before, during and at discharge of an emergency department visit.

Methods: We conducted a cross-sectional study to estimate the prevalence of PIM in a randomly selected sample of Chilean older adults aged ≥65 years attended in an ED of a high-complexity private clinic during 4 months of 2014. PIM was defined by 2012 Beers criteria, including diagnoses or conditions and drug to be used with caution. We estimated the prevalence of PIM before, during and at discharge of ED.

Results: A total of 400 patients and 5290 drugs were assessed in the study (2392, 348 and 2550 drugs before, during and at discharge of the ED). The mean age and SD was 73.2 ± 6.9 years, 66% were women and 69.5% had polypharmacy (five or more drugs) at discharge of the ED. Hypertension (16.9%) and dyslipidemia (12.3%) were the most frequent comorbidities. The main reason of the ED visit was pain (32.8%), and 71% of cases were classified as less urgent, triage level IV. The prevalence of PIM before, during and at discharge of the ED was 65.3%, 11.8% and 51.8%, respectively. The most common PIMs before and after the ED visit included psychotropic drugs (clonazepam (11.5%), sertraline (9.3%) and alprazolam (9.0%)) and NSAIDs (ketorolac, 43.4%) during the ED visit.

Conclusions: Even the prevalence of PIM during the ED visit was low; approximately one in two older adults received at least one PIM before and at discharge of the ED. Psychotropic drugs were found to have the highest potential for PIM. Additional studies should be conducted to know the potential adverse outcomes associated with the exposure of PIM during ED visit.

182. Potentially inappropriate medication among Chilean older inpatients: comparison between a 2012 Beers criteria and STOPP

Marcela Jirón,[1] Mariangel Tapia,[1] Tamara Sandoval,[1] Daniel Palma,[2] Sebastián Orellana,[1] Leslie Escobar,[1] Isabel Huala,[1] Elena Vega.[1] *[1]Ciencias y Tecnologia Farmaceutica, Facultad de Ciencias Quimicas y Farmaceuticas, University of Chile, Santiago, Chile [2]Unidad Geriatrica de Agudos, Hospital Clinico de la Universidad de Chile, Santiago, Chile*

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Background: Potentially inappropriate medications (PIM) increase the risk of adverse effects of drugs in older adults. Beers criteria (BC) and STOPP have been used internationally to identify PIM, but Chilean data are lacking.

Objectives: The aim of the study is to compare the prevalence of PIM among Chilean older inpatients using 2012 BC and STOPP.

Methods: We conducted a retrospective cohort study between 2006 and 2011 in a geriatrics unit (GU) of a teaching hospital in Chile. Medical records of a sample of patients aged ≥65 years were assessed. PIM was defined by 2012 BC and STOPP, including diagnoses or conditions. Drug to be used with caution was excluded. Functionality was measured using Barthel and Lawton tests. The effects of PIM over the length of stay (LOS), functionality and number of drugs used were also studied.

Results: A total of 347 patients were studied; 63.4% were female, and the mean age was 80.9 ± 7.6 years; 59.0% had polypharmacy (≥5 drugs) at admission. The mean LOS in the GU was 10.0 ± 7.3 days. The main reasons for admission to GU were geriatric management (11.5%) and delirium (3.2%). The prevalence of PIM was 64.8% according to 2012 BC and 47.0% according to STOPP. The most common PIMs were quetiapine (18.2%), haloperidol (12.4%) and furosemide (12.4%). Patients with at least one PIM according to 2012 BC had a significant increase of LOS (19.2% vs 38.7% stay >10 days; $p > 0.05$), and number of drug prescribed (30.6% vs 57.3% received >10 drugs; $p > 0.05$). Additionally, a significant decrease on instrumental daily living activities was found among patients receiving PIM compared with those without PIM ($p < 0.05$). There was no statistically difference with or without PIM on basic daily living activities according to 2012 BC and with or without PIM according to STOPP on functionality, and LOS.

Conclusions: The 2012 BC identified more PIM than STOPP in this sample of inpatient older adults. The prevalence of PIM found was higher than that of most of other studies. The effect of PIM on the LOS, number of drugs used and decreased functionality should be confirmed with additional studies.

183. Factors associated with medication errors in hospitalized patients in Chile

Ann-Loren Smith, Inés Ruiz, Marcela Jirón. *Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile*

Background: Medication errors (ME) increase the risk of adverse drug effects. Recognize risk factors associated with ME could help improve the quality and safety of healthcare.

Objectives: The aim was to determine the factors associated with ME among hospitalized patients.

Methods: A cross-sectional study was conducted in a randomly selected sample of patients admitted in an internal medicine service (MS) of a high-complexity public hospital of Chile. ME was detected using direct observation. Morbid and sociodemographic characteristics of the patients and the health care team characteristics were also collected. We determined independent determinants of ME and their 95% confidence intervals (CI) by using univariate and multivariate logistic models.

Results: A total of 225 patients were included during the study period. The mean ± SD age was 65.6 ± 16.3 years (61.8% of them were over 60 years old), 60.9% were women and 12.0% were hospitalized for stroke. The strongest predictor of EM was the administration time schedule (10 am; OR 3.5; 95%CI [1.9, 6.4]). EM was also independently associated with the administration of four or more drugs concurrently (OR 2.7; 95%CI [1.4, 5.1]), administration day (Thursday OR 2.5; 95%CI [1.2, 3.6]).

Among staff characteristics, sex and labour stability of the nurse technical staff were found risk factors of ME (OR 2.5; 95%IC [1.4, 4.3]) and (OR 2.8; 95%IC [1.7, 4.7]), respectively.

Conclusions: The identification of risk factors associated with ME could lead to prevent EM in hospitalized patients who are at risk for adverse effects. Future studies could implement strategies focused on drug administration process.

184. Effect of no technological interventions for reducing medication error

Ann-Loren Smith,[1] Inés Ruiz,[1] Tamara Yañez,[2] Mónica Catalán,[2] Marcela Jirón.[1] [1]*Facultad de*

Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile [2]Facultad de Farmacia, Universidad de Valparaíso, Valparaiso, Chile

Background: Medication errors (ME) increase the risk of adverse effects of drugs in the inpatient and were a major limiting the effectiveness and safety of pharmacological therapies in hospitalized patients.

Objectives: The aim was to determine the effect of a preventive intervention programme (PIP) in the error frequency of medicine service (MS) patients.

Methods: A quasi-experimental prospective before–after study was conducted in a randomly selected sample of 690 adult inpatient MS. An observational baseline and post-intervention assessment of the ME frequency was performed over a control group and a post-intervention group, respectively. Direct observation was used to detect ME. Each medication process was compared with what the prescriber ordered; if there was a difference, the error was described and categorized. A PIP (bundle of non-technological interventions to reduce ME, such as staff education and process standardization) was implemented between each phase. All medication prescriptions, transcriptions, dispensing, preparations and administrations were assessed before and after PIP by independent pharmacists. ME were defined according to the National Coordinating Council for Medication Error Reporting and Prevention.

Results: A total of 454 drugs for 225 control patients and 811 drugs for 465 post-intervention patients. The implementation of the PIP resulted in a 50.7% decrease on ME frequency (30.4–15.0%; $p < 0.05$). Main variations of ME frequency were seen in anticoagulant medications (70.1% of reduction) and administration process (46.6% of reduction).

Conclusions: The implementation of PIP based no technological strategies, such as training of technical personnel on safety and standardization of medication procedures resulted in a significant reduction of ME frequency at an adult MS.

185. Incidence of intravenous medication errors in a Chinese hospital

Qian Ding,[1] Kenneth Barker,[2] Elizabeth Flynn,[3] Ming Chang.[4] *[1]Pharmaceutical Sciences, Ferris State University, Big Rapids, MI, USA [2]Auburn University, Auburn, AL, USA [3]University of Florida, Gainesville, FL, USA [4]China Resources Purenhong Pharmaceutical Co., Ltd., Beijing, China.*

Background: China has an overwhelming usage of intravenous (IV) drugs compared with other countries. Given that serious and life-threatening IV medication error cases have been reported, the study of medication errors in Chinese hospital is still rare.

Objectives: The objectives were to explore and measure the frequency of IV medication errors by direct observation and identify clues to their causes in Chinese hospital inpatient wards.

Methods: A prospective study was conducted by direct observational method to describe IV medication errors on two general surgery patient wards in a large teaching hospital in Beijing, China. A trained observer accompanied nurses during IV preparation and administration procedures to detect medication errors. An IV medication error was defined as any ingredient observed which was mixed in the IV bag and administered to the patients, different from the interpretable physician's orders written on the patient charts. Total opportunities for error (T.O.E.s) were defined as the IV ingredients ordered by the physician and interpretable by the observer, plus unordered IV ingredients observed to be given to the patient. The detected medication errors were divided by the T.O.E.s and multiplied by 100 to obtain the medication error rate. Descriptive data of IV medication error rates were provided for each observation day.

Results: A final total of 589 ordered doses plus four unordered doses as prepared and administered to the patients were observed from 3 August to 13 August 2010. The overall IV medication error rate detected on the study wards in a Chinese hospital was 12.8% (76 errors of 593 T.O.E.s). Detected errors included ISMP's high-alert medications, such as insulin, potassium chloride for injection concentrate, and sodium chloride for injection concentrate. The most frequent errors by category were wrong dose (42%), wrong time (29%), omission (21%), unordered dose (5%), and extra dose (3%). Excluding wrong time errors, the IV medication error rate was 9.1%.

Conclusions: The results show that an average of about one IV medication error occurred in every 10 ingredients prepared by the trained nurses in a Chinese hospital.

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186. Prevalence and determinants of potentially inappropriate medication prescribing among older US adults according to STOPP criteria

Marcela Jirón,[1] Virginia Pate,[2] Laura C Hanson,[3] Michele Jonsson Funk,[2] Til Stürmer.[2] *[1]Ciencias y Tecnologia Farmaceutica, Facultad de Ciencias Quimicas y Farmaceuticas, University of Chile, Santiago, Chile [2]Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, NC, USA [3]Division of Geriatric Medicine, School of Medicine, University of North Carolina at Chapel Hill, NC, USA*

Background: Potentially inappropriate prescribing (PIP) increases the risk of adverse effects of drugs in older adults. Screening Tool of Older People's Prescriptions (STOPP) Criteria have been used in European countries to identify PIP, but there are no US data using these criteria.

Objectives: The aim is to assess the prevalence and determinants of PIP among US older population.

Methods: We used a national random sample of fee-for-service Medicare Parts A, B, and D beneficiaries from 2007 to 2012 to determine the 12-month prevalence and factors associated with PIP in the US population aged ≥65 years. PIP was defined by STOPP criteria, including diagnoses or conditions present in the previous calendar year. Polypharmacy was defined as five or more drugs prescribed in the same month. We assessed the determinants of PIP among adults filling ≥1 prescription using multivariable logistic regression models allowing for dependence of events.

Results: A total of 3 827 883 patients and 131 091 972 observations were included during the study period. The mean ± SD age was 77.4 ± 7.8 years, 66.1% were women, and 85.2% were White. Overall, the 12-month prevalence of PIM was 54.8% (95%CI [54.2, 55.4]). The strongest predictor of PIP was the number of drugs (10+ vs 1–2 drugs; OR 7.52; 95%CI [7.13, 7.93]) and polypharmacy (OR 3.53; 95%CI [3.44, 3.63]). PIP was also independently associated with female sex (OR 1.18; 95%CI [1.13, 1.23]), African American race (OR 1.19; 95%CI [1.11, 1.27]), the West (OR 1.11; 95%CI [1.04, 1.18]), and at least one emergency room visit during the previous 12 months (OR 1.10; 95%CI [1.07, 1.13]).

Conclusions: Approximately one in two older US adults received at least one PIM yearly. A higher number of drug claims per month and sociodemographic characteristics of the patient were associated with a higher likelihood of PIP. These findings suggest potential targets for new strategies to prevent PIP in older adults who are at risk for adverse effects.

187. Drug utilization and characteristics of new users of prucalopride in a UK primary care setting

Ana Ruigómez, Luis-Alberto García-Rodríguez. *Spanish Centre for Pharmacoepidemiological Research (CEIFE), Madrid, Spain*

Background: Knowledge of the prucalopride patient population is scarce in terms of its co-morbidity and concomitant medication profile, which can help contextualize spontaneous reports of adverse events.

Objectives: The objectives of the study were to characterize patients initiating prucalopride treatment in the UK and describe temporal changes in physician prescribing patterns in a UK primary care setting.

Methods: The Health Improvement Network (THIN) UK primary care database was used to identify all patients who received a first prescription of prucalopride between April 2010 and May 2014, and a comparison group of non-users individually matched by date, age and sex to the cohort of prucalopride users (5:1). Temporal changes in characteristics of users of prucalopride were analyzed comparing patients starting treatment in 2010–2011 vs 2012–2014.

Results: Among the 744 new prucalopride users identified, 95% were women, and initiation of use peaked at ages 30–49 years (47.1%). Constipation was the main indication, alone (55.6%) or with IBS (29.2%). Most patients (71%) were initially prescribed 2 mg once per day, for a mean duration of treatment episode of 206 days.

Prucalopride new users had higher level of health services use and of co-morbidity in particular gastrointestinal diseases (OR: 13.2, 95%CI [8.6, 20.3]) than the comparison group. They were also more likely to use other gastrointestinal medications. Depression and anxiety were also more common among prucalopride users.

Similar age and sex distribution was seen between the two periods, and prescription patterns did not change over time with constipation as the main indication.

Conclusions: This study shows that the patterns of prescription are in general agreement with the labelling recommendations among a cohort of new users of prucalopride in UK primary care. Patients initiating prucalopride had higher health care services use and had greater frequency of gastrointestinal comorbidity, as well as anxiety and depression. Similar prescription patterns and patients characteristics were seen over time.

188. Patterns of use of incretin-based therapies in Europe and USA

Ingrid Leal,[1] Cormac Sammon,[6] Gwen MC Masclee,[1] Giovanni Corrao,[2] Giorgia De Berardis,[3] Irene Bezemer,[4] Miguel Gil,[5] Elisa Martin,[5] Anita McGrogan,[6] Niklas Schmedt,[7] John D Seeger,[8] Gianluca Trifiro,[9,1] Serena Pecchioli,[10] Cristina Varas-Lorenzo,[11] Mark M Smits,[12] Peter Rijnbeek,[1] Miriam CJM Sturkenboom,[1] Silvana Romio.[1,2] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands [2]University Milano-Bicocca, Milano, Italy [3]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy [4]PHARMO Institute, Utrecht, The Netherlands [5]Spanish Agency for Drugs and Medical Devices, Madrid, Spain [6]University of Bath, Bath, UK [7]Leibniz-Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany [8]The Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA [9]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy [10]Health Search, Italian College of General Practitioners, Genomedics, Florence, Italy [11]RTI Health Solutions, Barcelona, Spain [12]VU University Medical Center, Amsterdam, The Netherlands*

Background: Incretin-based therapies (IBTs), dipeptidyl peptidase–IV inhibitors (DPP-4I) and glucagon-like peptide-1 receptor agonists (GLP-1RA) were introduced in the market in 2005–2006. Safety warnings, potential additional indications (e.g. obesity and pre-diabetes) or local policies could influence the patterns of use.

Objectives: The aim was to analyse the use of IBT in databases (DBs) participating in the SAFEGUARD project.

Methods: Prevalence (number of prevalent users/1000 person years [py]) and incidence (number of new users/1000 py) of use of GLP-1RA and DPP-4I in the DBs participating in the SAFEGUARD project (BIFAP (SP), GePaRD (DE), Regional DBs of Puglia and Lombardy, Health Search (IT), IPCI, PHARMO (NL), CPRD (UK) and Medicare (US)) were estimated across available time periods. The main characteristics of subjects (%, mean, standard deviation (s.d.) for categorical and continuous variables) at the time of the first prescription for an incretin-based agent were described. The study period ranged from 2005 to 2013 (DB specific).

Results: Sitagliptin (a DPP-4I) is the most commonly used IBT (prevalence in European (EU) DBs 0.05–0.76 and 18.4 users/1000 py in Medicare; incidence 0.05–0.54 users/1000 py in EU and 15.4/1000 py in Medicare). The use of liraglutide (a GLP-1RA) has steeply increased in all DBs. Sitagliptin and liraglutide use increased over the time in particular in the second half of 2010. The mean age of GLP-1RA new users is 48–56 years (yr) in EU DBs and 72 yr in Medicare; DPP-4I use starts at older ages (EU, 58–63 yr; Medicare, 75 yr). IBTs are frequently co-prescribed with biguanides (50–70%). In Medicare, 25% used TZD concomitantly with DPP-4I and 34% with GLP-1RA. This co-medication pattern was observed in less than 10% EU DB. Sulfonylureas and biguanides were the most commonly used antihyperglycemic agents before the start of IBT.

Conclusions: The use of incretin-based therapies has increased since they have been launched into the market. Sitagliptin, exenatide and liraglutide are the most frequently used. Their use starts at young ages.

189. Trends of use of non-insulin blood glucose lowering drugs in Europe and USA

Ingrid Leal,[1] Cormac Sammon,[6] Gwen MC Masclee,[1] Lorenza Scotti,[2] Giorgia De Berardis,[3] Irene Bezemer,[4] Miguel Gil,[5] Elisa Martin,[5] Anita McGrogan,[6] Niklas Schmedt,[7] John D Seeger,[8] Gianluca Trifiro,[1,9] Serena Pecchioli,[10] Cristina Varas-Lorenzo,[11] Mark M Smits,[12] Peter Rijnbeek,[1] Miriam CJM Sturkenboom,[1] Silvana Romio.[1,2] *[1]Erasmus University Medical Center, Rotterdam, The Netherlands [2]University Milano-Bicocca, Milano, Italy [3]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy [4]PHARMO Institute, Utrecht, The Netherlands [5]Spanish Agency for Drugs and Medical Devices, Madrid, Spain [6]University of Bath, Bath, UK [7]Leibniz-Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany [8]The Brigham and Women's Hospital, Harvard Medical*

School, Boston, MA, USA [9]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy [10]Health Search, Italian College of General Practitioners, Genomedics, Florence, Italy [11]RTI Health Solutions, Barcelona, Spain [12]VU University Medical Center, Amsterdam, The Netherlands

Background: New drugs for type 2 diabetes mellitus have been launched since the late 90s (meglitinides, thiazolidinediones (TZD), dipeptidyl peptidase–IV inhibitors (DPP-4I) and glucagon-like peptide-1 receptor agonists (GLP-1RA)). Safety warnings, potential additional indications or local policies could influence the patterns of use.

Objectives: The objective of the study was to describe the use of non-insulin blood glucose lowering drug (NIBGLD) agents in databases (DBs) participating in the SAFEGUARD project.

Methods: Prevalence (nr of prevalent users/1000 person years [py]) and incidence (nr of new users/1000 py) of use by year and age were estimated in nine DBs (BIFAP (SP), GePaRD (DE), Regional DBs of Puglia and Lombardy, Health Search (IT), IPCI, PHARMO (NL), CPRD (UK) and Medicare (US)) from 1998 to 2012 (DB specific) yearly and by age groups.

Results: Metformin had the highest prevalence (3.9–15.9 users/1000 py in European (EU) DBs and 170.6 users/1000 py in Medicare) and incidence (3.5–8.1/1000 py and 142.0/1000 py, respectively) followed by sulfonylureas. Sulfonylureas were preferred over metformin before 2002. The fixed combination metformin + sulfonylureas was consistently higher in the Italian DBs compared with the rest of DBs (3.0–4.9 vs. 0.1–0.9 users/1000 py) as well as the use of acarbose, which increased after 2009 only in the Italian DBs. The use of sulfonylureas decreased progressively with time, and TZD decreased after 2005–2007 in all DB, especially the incidence and mainly rosiglitazone. Sitagliptin and exenatide were the most frequently used incretin-based therapies. The use of all drugs increased with age, TZD and DPP-4I peak at early ages (70–75 years).

Conclusions: Metformin is the most prevalent NIBGLD agent, and its use increased in all DBs over time. The use of DPP-4I and GLP-1RA has increased after their introduction, while sulfonylureas and TZD decreased. Some patterns of use are country specific.

190. Survey on management of GERD: clinical experience with esomeprazole and levosulpiride

Mayuresh Fegade, Chetan Mehndiratta. *Medical Services, Ranbaxy Laboratories Limited, Mumbai, Maharashtra, India.*

Background: Gastroesophageal reflux disease (GERD) results from continued exposure of the esophageal mucosa to gastric secretions. A significant percentage of patients with GERD also have delayed gastric emptying. Though proton pump inhibitors (PPIs) are known to decrease acid secretion, they do not have any effect on the lower esophageal sphincter (LES) tone or gut motility. Hence, in patients not responding to PPI alone, addition of a prokinetic agent such as levosulpiride increases LES pressure and promotes gastric motility.

Objectives: This survey was aimed to determine the usage profile of fixed dose combination (FDC) of esomeprazole + levosulpiride and physician's clinical experience with it in the management of GERD.

Methods: This survey was conducted from July 2013 to December 2013 based on the clinical experience of 40 randomly selected physicians on an aggregate patient basis in the management of GERD from different parts of India. Prescription event monitoring (PEM) forms (maximum 10 forms per physician) comprising various objective questions were self administered to these physicians which were filled up by them. Patients diagnosed with GERD who were put on FDC of esomeprazole + levosulpiride were included in study. Data from 378 patients were analyzed.

Results: Of the 50 surveys mailed, we received 46 completed surveys (response rate: 92%). Responding physicians were general practitioners. Of the patients diagnosed with symptomatic GERD, 63% were males, and 37 % were females. Physicians observed that 100% of the patients got relief from symptoms at the end of treatment with fixed dose combination of esomeprazole + levosulpiride. Antacids were the most common co-prescribed drugs (in 7.67% patients). Adverse effects like loose motions and fever with headache were noticed in only 0.79% of patients.

Conclusions: This survey highlighted that addition of a prokinetic agent like levosulpiride with PPI esomeprazole offered better symptomatic relief in patients suffering from GERD. Physicians also opined that this combination is effective in management of GERD with good safety profile.

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191. 11 years of outpatient antibiotic utilization in Portugal – utilization pattern and regional comparison between 2004 and 2014

Marta V Gomes,[1,2] Carla Torre,[1] José Guerreiro,[1] Paulo Nogueira,[2] Cristina Furtado.[2] *[1]Centre for Health, Evaluation and Research (CEFAR), National Association of Pharmacies, Lisboa, Portugal [2]Institute of Preventive Medicine, Faculty of Medicine, University of Lisbon, Lisboa, Portugal*

Background: Portugal (PT), along with Southern European countries, is continuously ranked as the country where antibiotic (AB) use and quality improvement are most needed. National Program for Prevention and Control of Infection and Antimicrobial Resistance is one of the key national health programs, and an Intersectoral Alliance for the Preservation of Antibiotics was launched in 2011.

Objectives: The aim was to assess the quality and evolution of outpatient AB pattern use within Portuguese regions.

Methods: Outpatient systemic AB (ATC: J01) use and comparison between Portuguese seven regions (NUTS II: North, Centre, Lisbon, Alentejo, Algarve, Madeira and Azores), from 2004 to 2014. Data were retrieved from CEFAR Pharmacy Sales Information System, a representative nationwide sellout database for ambulatory care. Main outcome measure was the defined daily dose (DDD) per 1000 inhabitants per day (DHD). Quality of outpatient use was assessed through 12 European Surveillance of Antimicrobial Consumption (ESAC) drug quality indicators for outpatient AB use.

Results: Between 2004 and 2014, both total outpatient AB (J01) and quinolone (J01M) use decreased 11.5% and 28.1% in Portugal, respectively. J01 use, in 2014, varied between 19.9 DHD in Madeira and 23.7 DHD in Lisbon region. The highest reduction was observed in the Center region (18.1%). Cephalosporin consumption, in 2014, ranged from 1.0 DHD in North to 2.0 DHD in Algarve. Combination of penicillins (J01CR) increased in every region, ranging from 16.1% in Centre to 64.9% in Madeira. In 2014, broad–narrow spectrum ratio indicator had wide variation in the Portuguese territory, ranging from 17.2 in Azores to 65.5 in Madeira; the latter also had the highest increase (500%), over the study period.

Conclusions: Portuguese regions showed a high variation of AB consumption and ESAC quality indicators and evolution, over the study period. Assessing evolution and quality within national regions allowed detection of heterogeneous antibiotic pattern use within region, in order to focus interventions on critical regions.

192. Prevalence of prescription and dosage of antibiotics in outpatients from Mexico City: pilot study

Ramiro Sánchez-Huesca,[1,2] Jesús-Oswaldo García-Ávila,[2] Claudia Lerma.[1,3] *[1]Facultad de Ciencias de la Salud, Universidad Anáhuac México Norte, México City, DF, Mexico [2]Investigación en Medicina, CEBECI Farmacología Clínica, S.C., México City, DF, Mexico [3]Instrumentación Electromecánica, Instituto Nacional de Cardiología "Ignacio Chávez" México City, DF, Mexico*

Background: Since the restriction of over-the-counter dispensing of antibiotics in Mexico, there has been a decrease on the number of antibiotic retail sales. However, the antibiotic prescription patterns remain unknown, particularly among outpatients.

Objectives: The objectives are as follows: (i) to estimate the prevalence and prescribed daily dose (PDD) of antibiotics in outpatients from Mexico City and (ii) to compare PDD against the defined daily dose (DDD) as established by the World Health Organization (WHO).

Methods: This pilot study was retrospective, cross-sectional and descriptive. To gather antibiotics' information prescribed to outpatients, 108 recipes were obtained at a community drugstore of Mexico City. Each prescription was separately classified and analyzed by ATC/DDD system. Antibiotic prevalence was calculated, dividing the number of prescriptions for each antibiotic by the total prescription number. PDD was calculated by taking the average of the daily doses of the antibiotic drug. Median PDD values of each ATC class were compared with its corresponding DDD by Wilcoxon signed-rank tests. The PDD to DDD ratio was then calculated to determine sub-use (PDD/DDD < 1.0) or overuse (PDD/DDD > 1.0)

Results: A total of 108 prescriptions were analyzed. Prescription prevalence among antibiotic groups was higher for cephalosporins (27.8%), penicillins (26.9%), quinolones (17.6%), macrolides (10.2%) and tetracyclines (10.2%). Comparisons of median

PDD versus DDD from each ATC class with at least five prescriptions showed significant differences for amoxicillin ($p=0.02$), amoxicillin with clavulanate ($p<0.001$), azithromycin ($p=0.014$), levofloxacin ($p=0.02$) and tetracycline ($p=0.039$). Prescriptions with sub-use were more frequent among tetracyclines (63.6%), cephalosporins (36.7%), penicillins (24.1%) and quinolones (10.5%). In contrast, prescriptions with overuse were more frequent with macrolides (81.8%) followed by penicillins (65.5%) and quinolones (31.6%).

Conclusions: The prescriptions that have been analyzed in this pilot study suggest a wide variety of antibiotic use among outpatients in Mexico City. Most antibiotics with high prescription prevalence had also high-rated sub-use or overuse.

193. Survey to understand role of angiotensin receptor blockers (ARBs) in the management of hypertension

Mayuresh Fegade, Chetan Mehndiratta. *Medical Services, Ranbaxy Laboratories Limited, Mumbai, Maharashtra, India*

Background: The manner in which blood pressure (BP) is reduced influences outcome, and antihypertensive therapy should induce smooth and sustained BP control throughout the 24-h dosing interval. The studies also suggest that, in order to improve the cardiovascular risk profile of patients with hypertension, optimal antihypertensive therapy should provide sustained BP reduction and smooth BP control over the full 24-h period. In the patients treated with losartan, measurement of blood pressure at trough (24-h post-dose) relative to peak (5–6-h post-dose) demonstrated relatively smooth BP reduction over 24 h.

Objectives: This survey was aimed to determine the usage profile of different angiotensin receptor blockers (ARBs) in hypertension and physician's clinical experience with these ARBs in the management of hypertension.

Methods: This survey was based on the clinical experience of 43 randomly selected physicians on an aggregate patient basis in the management of hypertension from different parts of India. Prescription research survey (PRS) questionnaire forms comprising various questions were filled up by these physicians based on their clinical experience.

Results: Fifty-two percentage of all hypertensive patients taking medications are on ARBs. Majority (57.5%) of physicians use ARBs as the first line of therapy for newly diagnosed hypertensive patients. Losartan is a preferred ARB by most of the physicians (69.77%). Physicians also opined that smooth reduction of blood pressure is the most important factor in choosing antihypertensive drug followed by safety of the drug. Sixty-nine percent of physicians perceived losartan for smooth reduction of BP.

Conclusions: This survey highlighted that smooth reduction of blood pressure is the most important factor in choosing antihypertensive drug in hypertension. Losartan is the preferred drug for smooth reduction of BP.

194. Prescription profile of cefpodoxime proxetil in patients with various infections

Mayuresh Fegade, Chetan Mehndiratta, Jejoe KaranKumar. *Medical Services, Ranbaxy Laboratories Limited, Mumbai, Maharashtra, India*

Background: Cefpodoxime proxetil has a well-established antibacterial efficacy and safety profile in patients of all ages against a broad range of bacteria as established by numerous clinical studies. Post-marketing monitoring (PEM) of products is important for establishing the long-term use and safety in different populations.

Objectives: The aims of the study were to evaluate the factors associated with cefpodixime's use and determine the type of bacterial infections for which it is most commonly prescribed.

Methods: We conducted a retrospective cohort study conducted among patients prescribed cefpodoxime in a variety of outpatient practices in India. The primary outcome was a new prescription for cefpodoxime. The participating physicians filled up a questionnaire provided to them in an PEM form (maximum 10 per physician). A total of 869 patient's data were included for the analysis, and the current study describes these results.

Results: The average age of the patients was 34.81 ± 16.51 years with a range of 1–78 years. Out of the total 827 patients treated with cefpodoxime for whom

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are available, the majority (821, 99.3%) of the patients reported relief from the infection-associated symptoms. Among the different bacterial infections which were treated with cefpodoxime, respiratory tract infections caused by bacteria were the most common. A total number of 18 adverse events have been reported by 13 patients (1.5%) out of the total cefpodoxime-treated patients. The most commonly reported adverse event was nausea in five patients.

Conclusions: The efficacy and safety of cefpodoxime proxetil have been established in controlled settings of clinical trials, and this PEM further supports these findings in real-world clinical settings. In conclusion, Cefpodoxime is a broad spectrum antibiotic with good efficacy and safety in patients of all age groups.

195. Did the introduction of mandatory offer of generic substitution have a quantifiable effect in South Africa?

Andrew L Gray,[1] Yared Santa-Ana-Tellez,[2] Veronika J Wirtz.[3] *[1]Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Durban, South Africa [2]WHO Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands [3]Department of Global Health, Center for Global Health and Development, Boston University, Boston, MA, USA*

Background: Mandatory offer of generic substitution was implemented in the South African private sector in April 2003. We hypothesised that this legal change would result in quantifiable changes in generic and originator consumption, notably for chronic medication.

Objectives: The study aimed to assess the impact of the change in generic substitution policy on private sector sales of generic and originator medicines for chronic diseases.

Methods: Private sector sale data (June 2001 to May 2005) were obtained from IMS Health for proton pump inhibitors (PPIs; ATC code A02BC), HMG CoA reductase inhibitors (statins; C10AA), dihydropyridine calcium antagonists (C08CA), angiotensin converting enzyme inhibitors (ACE-I; C09AA) and selective serotonin reuptake inhibitors (SSRIs; N06AB). Monthly sales were expressed as defined daily doses per 1000 insured population per day (DDD/TID). Interrupted time series models were used to estimate the changes in slope and level of medicines use after the policy change. ARIMA models were used to correct for autocorrelation and stationarity.

Results: Only in the case of SSRIs was a quantifiable increase in the level of generic products (0.2 DDD/TID; p0.000), with a decrease in originator utilisation (-0.1; $p < 0.000$), detectable after the implementation of the policy. Contrary to expectations, utilisation of generic PPIs decreased by 0.01 DDD/TID ($p < 0.000$), while the use of originator products increased by 0.04 ($p = 0.002$). Over the same time period, the utilisation of generic calcium antagonists decreased by 0.05 DDD/TID ($p = 0.017$), while the use of the originator products increased by 0.04 ($p = 0.047$). The utilisation of originator ACE-I increased by 0.09 DDD/TID ($p < 0.000$), while the change in the level of generic ACE-I was not significant. No significant changes in statin utilisation were detectable. Changes in slope of usage were minimal for all pharmacological groups tracked.

Conclusions: Mandatory offer of generic substitution appeared to have had minimal effect on utilisation patterns in the 2 years after 2003, perhaps as other managed care interventions were already in place, but remains an important enabling provision.

196. Identifying potential spill-over effects of the Maryland prescription drug monitoring program

Ting-Ying Huang, Patience Moyo, Sarah Tom, Linda Simoni-Wastila. *Pharmaceutical Health Services Research, University of Maryland Baltimore, Baltimore, MD, USA*

Background: Evidence suggests statewide prescription drug monitoring programs (PDMPs) may increase cross-border prescription fills for controlled medications in neighboring states. In August 2013, Maryland implemented a PDMP, which provided an opportunity to examine spillover of prescription fills and associated spatial patterns.

Objectives: The study aimed to identify potential PDMP spillover in Schedule II prescription fills between Maryland and neighboring states.

Methods: This ecological study used 2012–2013 IMS Health Schedule II prescription fill data collected from

retail pharmacies in metropolitan statistical areas (MSAs) within or connected to Maryland ($n = 19$). Data included the total number of prescription fills by drug name, state-specific MSA and month. Monthly changes in prescription fills from 2012 to 2013 were calculated and examined with spatial autocorrelation and space–time analysis using bivariate Moran's I and local indicator of spatial association (LISA). All analyses were conducted using ArcGIS® and GeoDa.

Results: Average change in monthly prescription fills ranged from –3.31% to +3.78%. Negative spatial autocorrelation was observed in every study month. However, spatial clustering was not statistically significant until December ($I = -0.30$, $p = 0.02$). LISA results indicated high–low clustering (high local changes surrounded by low neighbor changes in prescription fills, $p < 0.05$) in Cumberland, WV, USA, and Hagerstown-Martinsburg, WV, USA, and low-low clustering in Hagerstown-Martinsburg, MD, USA starting from July. Space–time analyses using varying time lag in months returned similar spatial autocorrelation and local clustering patterns. Spatial clustering was negatively significant when lagging changes in prescription fills in September ($I = -0.30$, $p = 0.02$) and October ($I = -0.30$, $p = 0.02$) to December.

Conclusions: Spillover effects of the Maryland PDMP on Schedule II prescription fills were identified in West Virginia. Anticipatory effects may occur as early as 2 months before PDMP phases. Spatial patterns in prescription fill changes could take 2–3 months to form.

197. Spontaneous adverse event reports associated with apixaban and potentially inappropriate medicine use: an international comparison

Gillian E Caughey, Lisa M Kalisch Ellett, John D Barratt. *Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia*

Background: Apixaban is a new oral anticoagulant recently approved for prevention of stroke in patients with atrial fibrillation or prophylaxis of deep vein thrombosis after knee or hip replacement. Recent meta-analyses have been inconclusive with regard to risk of bleeding compared with warfarin. Safety concerns remain regarding apixaban's potential to increase bleeding risk and the current lack of an antidote to reverse its anticoagulant effects.

Objectives: The study aimed to analyse spontaneous adverse event reports associated with apixaban from Australia, Canada and the USA and to examine potentially inappropriate concomitant medicine use which may place patients at increased risk of adverse events.

Methods: Spontaneous adverse event national databases from Australia, Canada and the USA were used to examine reports of adverse events associated with apixaban from 1 January 2012 to 30 September 2014. Disproportionality analyses including proportional reporting ratio (PRR) and reporting odds ratio (ROR) were conducted for the quantitative detection of signals using the USA database. Concomitant medicine use was also identified from reports.

Results: Haemorrhage was the most common reported adverse event, ranging from 26% of reports for Australia to 30.9% for Canada. Gastrointestinal (GI) haemorrhage accounted for 36.7% of Australian, 50% of Canadian and 58.8% of the USA haemorrhage adverse event reports. Positive signals were confirmed in the USA data (all haemorrhage: PRR 4.03, $\chi 2$ 36.11 and ROR 4.16, 95%CI [2.6, 6.8]; GI haemorrhage: PRR 5.7, $\chi 2$ 34.35 and ROR 5.81, 95%CI [3.1, 10.9]). Across all three countries, almost half of all adverse events for apixaban reported concomitant use of medicines with the potential to increase bleeding risk, ranging from 47.6% in Canada to 65.5% in Australia.

Conclusions: A large proportion of adverse events for apixaban were associated with concomitant medicine use, which may have placed the patient at increased risk of adverse events, in particular haemorrhage. Increased awareness of patients' comorbidity and associated medicine use is required to minimise risk and ensure the safe and effective use of apixaban in clinical practice.

198. Patterns of intravenous corticosteroid utilization in patients undergoing coronary artery bypass grafting surgery in the USA

Macarius M Donneyong, Joshua J Gagne. *Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA*

Background: Corticosteroids reduce the risk of atrial fibrillation in patients undergoing coronary artery bypass graft (CABG) surgery, but their impact on

mortality and safety outcomes is uncertain. The extent to which providers have adopted the use of perioperative corticosteroids in CABG is unknown.

Objectives: The aims of the study were to assess trends in use of perioperative intravenous corticosteroids (IVCS) in CABG surgery, to identify factors that predict their use, and to explore between-provider variation in use.

Methods: Using a nationally representative US inpatient database, we identified patients who underwent CABG, 2003–2011. We determined the proportion of CABGs in which IVCS were administered on the day of surgery. Linear time-series models were used to estimate the rate and trend of IVCS use over time. Separate multivariable generalized estimating equation models were then used to identify the predictors of perioperative IVCS use, while accounting for clustering at the provider level. We also quantified IVCS utilization by the top and bottom quartiles of providers who administered IVCS.

Results: Of the 297 441 eligible CABGs, 58 308 (20%) involved IVCS administration on the day of surgery; of these, 46% used methylprednisolone, 34% used dexamethasone, and 20% used hydrocortisone. Use of IVCS increased 0.51% (95%CI [0.35, 0.67]) per year from 2003 to 2011. Native Americans were more likely (OR: 1.39; 95%CI [1.02, 1.91]) to receive IVCS than Whites. Older age groups, compared with those <45 years, were more likely to receive a perioperative IVCS. Receipt of H2 blockers, heparin, loop diuretics, and vitamin K was associated with IVCS administration. Patients were less likely to receive IVCS if they had an echocardiogram prior to surgery. Of the 422 institutions that performed more than 10 CABGs, the top quartile institutions administered IVCS in ≥36.3% of CABGs, and in the bottom quartile, providers administered IVCS in ≤3.4% of CABGs.

Conclusions: Despite an unclear risk–benefit tradeoff, IVCS administration during CABG has increased gradually since 2003. A large-scale study to assess the multiple potential harms and benefits of this practice is warranted.

199. Antiepileptic drug utilization across 15 years for epilepsy and non-epilepsy indications in a Canadian province: a population-based study

Christine Leong,[1] Muhammad M Mamdani,[2,3,4,5,6] Tara Gomes,[3,4,5,6,8] David N Juurlink,[3,7,9,10,11] Erin M Macdonald,[3] Marina Yogendran.[12] *[1]College of Pharmacy, University of Manitoba, Winnipeg, MB, Canada [2]Applied Health Research Centre, St. Michael's Hospital, Toronto, ON, Canada [3]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada [4]Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON, Canada [5]Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada [6]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada [7]Schulich Heart Research Program, Sunnybrook Research Institute, Toronto, ON, Canada [8]Ontario Drug Policy Research Network, Toronto, ON, Canada [9]Departments of Medicine and Pediatrics, University of Toronto, Toronto, ON, Canada [10]Divisions of General Internal Medicine and Clinical Pharmacology, Sunnybrook, Toronto, ON, Canada [11]Ontario Poison Information Centre, Hospital for Sick Children, Toronto, ON, Canada [12]Department of Community Health Sciences, Manitoba Centre for Health Policy/University of Manitoba, Winnipeg, MB, Canada*

Background: Recent evidence suggests a growing use of antiepileptic agents for the management of non-epileptic conditions such as pain, mood and anxiety disorders. The extent of growth of antiepileptic drug (AED) utilization for non-seizure indications in Canada is unknown.

Objectives: The study aimed to examine trends in AED use among individuals living in Manitoba with and without a history of epilepsy.

Methods: The quarterly prevalence in AED users between 1998 and 2013 among individuals with and without a history of epilepsy was assessed using a cross-sectional time series analysis with data obtained from the administrative health databases at the Manitoba Centre for Health Policy. Epilepsy was defined as at least three physician claims (separated by more than 30 days) or one hospitalization (ICD-9 345) within 2 years from the beginning of each quarter.

Results: The number of individuals who used AEDs increased more than three-fold from 8883 to 27 246 over the study period. The prevalence of AED use among patients with epilepsy increased by 3% from 789.6 per 1000 in the first fiscal quarter of 1998/1999 to 813.9 per 1000 in the last fiscal quarter of 2012/2013 ($p < 0.001$ after 2006). In contrast, a 210% increase in AED use was observed among patients without epilepsy from 6.8 to 21.1 per 1000

over the same period ($p < 0.001$). Users of newer AEDs increased from 0.3 to 15.0 per 1000 ($p < 0.001$), and users of older AEDs decreased slightly from 7.5 to 6.4 per 1000 ($p < 0.001$) from 1998/1999 to 2012/2013. There was a 55-fold rise in gabapentin use among non-epilepsy users from 0.2 to 11.1 per 1000, while gabapentin use among those with epilepsy only increased nearly two-fold from 21.6 to 41.3 per 1000.

Conclusions: There has been a marked increase in the prevalence of antiepileptic drug users over the last 15 years, with a large shift towards the use of newer antiepileptic agents, primarily gabapentin, among those without epilepsy. The efficacy of some newer AEDs used off-label for specific non-seizure conditions remains inconclusive. Future research on the impact of these trends on health and economic outcomes will be of interest to policymakers.

200. Trends in the consumption of antiepileptic drugs in Portugal, 2004–2014

Carla Torre, Jose Pedro Guerreiro, Marta Gomes, Suzete Costa. *Centre for Health Evaluation and Research (CEFAR), National Association of Pharmacies, Lisboa, Portugal*

Background: Antiepileptic (AE) drugs represent the main therapeutic approach for epilepsy, but labelled indications also include neuropathic pain, bipolar disorder and anxiety, among others. It is reported that AE off-label use is increasing worldwide. In Portugal, despite the introduction of new AE in recent years, the changes in consumption patterns remain poorly documented.

Objectives: The aim of the study was to determine the trends in the consumption of AE in Portugal over the last 11-year period (2004–2014).

Methods: Drug consumption data (pharmacological subgroup: N03A) was estimated for the study period through CEFAR Pharmacy Sales Information System, a nationwide database with representative drug-dispensing data from ambulatory care at a regional level. Main outcome measure was the defined daily dose (DDD) per 1000 inhabitants per day (DHD). Total costs in euro and the cost/DDD were calculated. Linear regression model was set up to investigate the trends in the use of AE. A GLM model was adjusted to explore regional asymmetries in drug consumption.

Results: Total AE consumption increased linearly (beta = 0.76; R2 = 0.98; $p < 0.0001$) from 9.7 DHD in 2004 to 17.3 DHD in 2014 (total growth of 78.7%), mainly due to new drugs. Valproic acid had the highest consumption in 2014 (3.3 DHD), followed by pregabalin (3.2 DHD), which showed a rapid uptake since 2005. Carbamazepine decreased 21.0% over the study period (1.9 DHD in 2014). Total expenditure rose from 46M€ to 78M€. In 2014, pregabalin was responsible for 42.8% and 18.3% of total costs and DDD, respectively. Despite the growth of generic market share (4.0% in 2004 to 28.7% in 2014), the overall cost/DDD had a small decrease from 1.25€ to 1.19€ due to the growth in the consumption of newer and more expensive drugs. Regional differences were found ($p < 0.0001$).

Conclusions: Portuguese overall AE consumption rose by 78.7% over the study period, which might represent an increasingly use, namely for pregabalin, for indications apart epilepsy. Although in 2014, the volume share of the newest AE (e.g. rufinamide and eslicarbazepine) was still modest, their introduction has led to a strong increase in the cost, which emphasize the need of cost-effectiveness studies using real-world data.

201. National use of testosterone replacement therapy: annual trends and response to recent evidence

Eleanor Lucas,[1] Matthew Daubresse,[1] Sonal Singh,[1] Randall Stafford,[2] G Caleb Alexander.[1] *[1]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA [2]Program on Prevention Outcomes and Practices, Stanford Prevention Research Center, Palo Alto, CA, USA*

Background: During the past decade, several new products and non-injectable formulations of testosterone have been developed and promoted. Despite this, use of testosterone replacement therapy is controversial, particularly for men with mildly depressed testosterone levels or non-specific symptoms such as sexual dysfunction or fatigue.

Objectives: The study aimed to quantify the utilization and marketing of testosterone replacement therapies in the United States, including the impact of recently emerging safety signals.

Methods: Descriptive analyses of IMS Health's National Disease and Therapeutic Index, a nationally representative audit of ambulatory practice, and IMS Health's Integrated Promotional Services database, which provides national estimates of physician and consumer-targeted marketing and promotion. Outcome measures included the following: (1) quarterly testosterone drug uses and (2) quarterly provider and direct-to-consumer (DTCA) promotional spending for these products.

Results: In 2003, there were 0.79-million [M] (95% confidence intervals [CI] [0.55, 1] M) product uses in the United States. Use remained stable until 2007Q1 and, between this point and 2013Q3, increased steadily at 9% per year, reaching 2.0-M (CI [1.5, 2.5] M) annual uses by 2013. Since 2013Q3, use has declined by more than 40%, from a peak of 0.51-M (0.39–0.63 M) quarterly uses in 2013Q3 to a nadir of 0.29-M quarterly uses (0.16–0.42 M) in 2014Q4. Between 2003 and 2014, there were large increases in the proportion of uses reported by primary care physicians, as well as large differences in utilization by male vs. female physicians, with male physicians accounting 86–94% of all uses during the study period. Quarterly total promotion was approximately $5–16 M between 2009Q1 and 2011Q1, before increasing more than three-fold to a maximum of $65 M during 2013Q2, driven mainly by DTCA, and declining precipitously during 2014Q4 to $5 M.

Conclusions: There have been remarkable increases and, more recently, decreases in the use of testosterone replacement therapies in the United States, reflecting the effects of marketing and promotion as well as emerging concerns regarding their safety and overall risk/benefit balance.

202. Risk of fall injury associated with psychotropic drugs among people aged 65 years or older in Sweden

Annica Bergendal, Pinelopi Lundquist, Julius Collin, Gudrun Jonasdottir Bergman, Peter Salmi, Natalia Borg, Bengt Danielsson. *The National Board of Health and Welfare, Rålambsvägen 3, Stockholm, Sweden*

Background: Elderly persons have a high prescription of psychotrophic drugs, often in combination.

Objectives: The aim was to assess the risk of fall injury associated with psychotropic drugs in single use and in combination among people aged 65 years or older.

Methods: This study is a register-based case-control study performed using Swedish national health register data. Cases were individuals, 65 years or older, hospitalized due to fall injury during 2011–2012. Diagnoses of fall injury (S72.0–72.4) were defined according to ICD-10 system and identified in the Swedish National Patient Register. The date of admission was used as the index date for both cases and controls. For each case, five aged-matched controls were randomly selected from the Swedish population register. To assess drug exposure 90 days before the index date, data on dispensed drugs were extracted from the Swedish prescribed drug register. Studied drugs were classified according to the Anatomical Theraputic Chemical (ATC) system, and the following groups were included, opioids (N02A), anxiolytics (N05B), hypnotics and sedatives (N05C) and antidepressants (N06A)

Associations were assessed by conditional logistic regression analyses adjusting for sex, level of education, Charlson comorbidity index, number of days in hospital care 12 months before the index date and use of studied drugs. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: We included 83 334 cases and 416 670 controls, 40% of cases were 85 years or older and two-thirds were women. Use of opioids or antidepressants was associated with increased risks of fall injury, OR 1.7 (95%CI [1.6, 1.7]) and OR 1.5 (95%CI [1.5, 1.6]), respectively. The risk of fall injury was less pronounced among users of hypnotics, OR 1.2 (95%CI [1.2, 1.3]), or anxiolytics, OR 1.3 (95%CI [1.2, 1.3]). For users of both opioids and antidepressants in combination, the OR was 2.1 (95%CI [2.0, 2.3]).

Conclusions: Use of psychotropic drugs among individuals older than 65 years is associated with increased risk of hospitalization due to fall injury. Opioids and antidepressants were associated with the highest risks, both in single use and in combination.

203. Treatment patterns and characteristics of postmenopausal women with HR+/HER2− metastatic breast cancer receiving everolimus

Francis Vekeman,[1] Yanni Hao,[2] Wendy Y Cheng,[3] Jonathan Fortier,[1] Marie-Noëlle Robitaille,[1] Mei Sheng Duh.[3] *[1]Groupe d'Analyse, Ltée, Montréal,*

QC, Canada [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA [3]Analysis Group, Inc., Boston, MA, USA

Background: The use of everolimus (EVE) in combination with exemestane in postmenopausal women with HR+/HER2− metastatic breast cancer (mBC) has been studied in clinical trials, yet little is known of its real-world utilization.

Objectives: We aimed to characterize the treatment patterns and characteristics of HR+/HER2− mBC patients (pts) with first-line endocrine therapy (Tx), who ever vs. never used EVE in real-world settings.

Methods: Data were from a community oncology electronic medical record database from Altos Solutions, Inc. Eligible pts were postmenopausal women, with ≥1 medical record with a BC diagnosis, confirmed HR+/HER2− status, first mBC diagnosis after 1 July 2012, and received first-line endocrine Tx. Characteristics of pts who ever vs. never received EVE were compared. Potential predictors of EVE use, including age at index date and at first breast cancer diagnosis, race, region, insurance type, metastatic sites, ECOG performance status, and disease recurrence, were assessed using logistic regressions.

Results: Of the 676 pts who met the inclusion criteria, 83 (12%) ever received EVE vs. 593 (88%) never. EVE was initiated primarily in second line (42.2%), followed by first line (41.0%), third line (10.8%), and fourth line and above (6%). Patients receiving EVE were younger at first mBC diagnosis (mean, 62 vs. 69 years; $p < 0.001$) and at first BC diagnosis (58 vs. 66 years; $p < 0.001$). Distribution of ECOG was similar between the two cohorts. Controlling for other characteristics, age was a significant predictor of EVE use in first-line Tx (odds ratio: 0.95, $p = 0.003$), but not in later lines. While not statistically significant, patients with higher ECOG were more likely to receive EVE in first line, and not in later lines. Patients with bone metastases were less likely to receive EVE in first line, but more likely in second line and above. Insurance type was not a predictor of EVE use.

Conclusions: EVE is typically used in second line in pts with HR+/HER2− mBC with first-line endocrine Tx. Patients who start EVE earlier tend to be younger with worse prognosis for mBC. Studies with larger sample sizes are needed to further characterize EVE pts and assess their treatment outcomes.

204. Nationwide time trend analysis of cancer targeted therapies in Taiwan (2009–2016)

Jason C Hsu,[1] Yea-Huei Kao Yang,[1] Jin-Ding Huang,[1] Christine Y Lu.[2] *[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA*

Background: Targeted therapies have been listed and reimbursed for treatment of malignancies by Taiwan National Health Insurance in recent years.

Objectives: This study examined the trends in use and expenditures of antineoplastic agents for treatment of all malignancies in Taiwan from 2009 to 2012. We also estimated the prescribing rate and market share of targeted therapies up to 2016 based on the existing trends.

Methods: The monthly claims data for antineoplastic agents between 2009 and 2012 were retrieved from Taiwan's National Health Insurance Research Database. We calculated the number of prescriptions and reimbursed costs for each class of medication and analyzed their time trends. In addition, using a time series design with ARIMA models, we estimated the prescribing rate and market share of targeted therapies for years 2015 and 2016.

Results: Among all antineoplastic agents, prescribing rate of targeted therapies grew from 6.24% in 2009 to 12.29% in 2012, and the market share of targeted therapies rose from 26.16% in 2009 to 41.57% in 2012. Especially, market shares of monoclonal antibodies and protein kinase inhibitors increased rapidly from 14.63% to 23.84% and from 10.71% to 16.12%, respectively. The prescribing rate and market share of targeted therapies were predicted to increase continuously and reach 19.33% and 61.59% by the fourth quarter in 2016, respectively.

Conclusions: Our findings indicate that, compared with other classes of antineoplastic agents, targeted therapies have played an increasing and more important role in treatment of all malignancies in Taiwan

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and they are likely to pose an even greater economic burden in the future.

205. Which types of cancer account for the highest use of targeted therapies in Taiwan?

Jason C Hsu,[1] Yea-Huei Kao Yang,[1] Jin-Ding Huang,[1] Christine Y Lu.[2] *[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA*

Background: Use of cancer targeted therapies has improved cancer survival and the quality of cancer care, but these innovative and expensive drugs have led to increases in pharmaceutical expenditures, representing an enormous economic burden. Little is known about the use of cancer targeted therapies in Taiwan.

Objectives: This study aimed to examine the current utilization of targeted therapies for treatment of different types of malignancies in Taiwan and determine which cancer types account for the highest use of targeted therapies.

Methods: We retrieved targeted therapies for all malignancies in 2009–2012 monthly claims data from National Health Insurance Research Database. We then calculated yearly number of users, number of prescriptions and reimbursed costs for targeted therapies by 20 common types of malignancy and analyzed their time trends. We also used one-way ANOVA method to explore the association between types of malignancy and targeted therapy use.

Results: Our analysis showed that the number of users, number of prescriptions and reimbursed costs for targeted therapies differed substantially between different types of malignancy. In 2012, the three types of malignancy that accounted for the highest use of targeted therapies in order were malignancies of (1) trachea, bronchus and lung, (2) female breast and (3) colon, rectum, rectosigmoid junction and anus. These three cancer types accounted for 28.21%, 14.1% and 12.82% of users of targeted therapies in 2012, respectively; 31.77%, 12.01% and 11.76% of prescriptions for targeted therapies; and 19%, 18.65% and 12.26% of reimbursed costs for targeted therapies.

Conclusions: Our analysis determined the present patterns of targeted therapy use for the selected 20 types of malignancies in Taiwan. Given the high costs of targeted therapies and their increasing availability, our results help identify the cancer types that are likely the main drivers of economic burden of pharmaceutical expenditures in health insurance system.

206. Geographic variations in use of cancer targeted therapies in Taiwan

Jason C Hsu,[1] Yea-Huei Kao Yang,[1] Jin-Ding Huang,[1] Christine Y Lu.[2] *[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA*

Background: Cancer targeted therapies have been used in Taiwan for several years, but little is known about their patterns of use, particularly variations in use by geographic regions.

Objectives: This study aimed to examine the current utilization of cancer targeted therapies by geographic regions (northern, midwestern, southern and eastern) in Taiwan in order to determine whether regional disparities in use exist.

Methods: This study used 2009–2012 monthly claims data for antineoplastic agents from Taiwan's National Health Insurance Research Database. Yearly number of users, number of prescriptions, reimbursed costs and growth rates of cancer targeted therapies were estimated for different regions in Taiwan. We also used one-way ANOVA method to explore the association between geographic variation and quantity and growth of targeted therapy use quarterly.

Results: Approximately 80% of targeted therapies were prescribed in northern and southern Taiwan from 2009 to 2012. In 2012, northern region accounted for the highest use of targeted therapies (49.39%), followed by southern (30.29%) and midwestern (18.91%), and eastern accounted for the lowest use (1.4%). In general, the yearly growth rates in use of targeted therapies by prescription volume (2009–2012) are similar between regions (northern 52.84%, midwestern 51.4%, southern 48.61% and eastern 47.6%). Our ANOVA analysis showed that the number of users, number of prescriptions and

reimbursed costs for targeted therapies differed substantially between regions. However, utilization growth rates are similar between regions over the study period.

Conclusions: Use of cancer targeted therapies varied substantially across regions of Taiwan. Northern and southern regions accounted for predominant use of cancer targeted therapies. Our study suggests a need for further investigation of whether regional disparities in access to cancer targeted therapies exist.

207. Utilization and Trends of Molecularly Targeted Therapies in Cancer Treatment: A 2006-2010 NAMCS Analysis

Donna R Rivera, Kelly Filipski, Andrew N Freedman. *Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, MD, USA*

Background: The rapid development of molecularly targeted therapies (MTTx) brings the promise of unparalleled possibilities for the future of personalized medicine in cancer treatment, with 10 new medications approved last year alone. There are currently 53 FDA-approved MTTx, spanning multiple drug classes: monoclonal antibodies, tyrosine kinase inhibitors, anti-VEGF therapies, mTOR inhibitors, and PARP inhibitors. Few studies explore the utilization patterns and adverse event-related medical visits associated with these therapies.

Objectives: The study aimed to explore the utilization patterns of selected MTTx in the treatment of breast cancer, non-small cell lung cancer, colorectal cancer, CLL, and NHL in the ambulatory care setting, through the use of patient and practice/provider characteristics, as well as analyzing indications, adverse events, and comorbidities to review appropriate use.

Methods: The National Ambulatory Medical Care Survey (NAMCS) provides a national probability sample using data from physicians about ambulatory care practice in the United States. The study includes 5 years of data from 2006 to 2010, allowing for measurement of trends in use as the therapeutic options increase. Relevant variables for inclusion are as follows: demographics, insurance, diagnoses, medications, practice/provider characteristics, cancer and staging, comorbidities, and health education. Analyses include the use of chi-square tests and multivariate logistic regression.

Results: We found 11 464 visits associated with patients identified as having cancer, representing 278 016 362 visits from 2006 to 2010. The weighted sample represents over 3.3-million visits, which involve the use of MTTx. The most frequently reported therapies are rituximab (23.19%), trastuzumab (21.71%),and bevacizumab (15.75%). In-depth analyses to explore utilization patterns including comparisons with traditional therapies are planned.

Conclusions: The use of molecularly targeted therapies is growing and changing the landscape of cancer treatment and patient care. It is essential to evaluate the factors associated with MTTx and the differences in cancer treatment practices across the United States.

208. Impact of cancer diagnosis and treatment on glycaemic control among individuals with colorectal cancer using glucose lowering drugs

Marjolein Zanders,[1] Myrthe van Herk-Sukel,[2] Ron Herings,[2] Lonneke van de Poll-Franse,[1,3] Harm Haak.[4,5] *[1]Netherlands Comprehensive Cancer Organisation, Eindhoven, The Netherlands [2]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands [3]CoRPS- Centre of Research on Psychology in Somatic Diseases, Tilburg, The Netherlands [4]Máxima Medical Centre, Veldhoven, The Netherlands [5]Maastricht University Medical Centre +, Maastricht, The Netherlands*

Background: Cancer patients with diabetes have a significantly higher overall mortality risk compared with patients without diabetes. Most research on diabetes and cancer has focussed on the influence of diabetes and glucose lowering drugs (GLDs) on outcomes after cancer diagnosis, yet cancer itself and the treatment of cancer might affect outcomes associated with diabetes, in part by affecting diabetes control.

Objectives: In our ambition to understand the association between diabetes, cancer and outcomes, this study aims to evaluate the impact of cancer and its treatment on HbA_{1c}-values among individuals with colorectal cancer (CRC) using GLDs.

Methods: Patients with primary CRC (1998–2011) were selected from Eindhoven Cancer Registry and

linked to the PHARMO Database Network including outpatient pharmacy and clinical laboratory data. Patients with more than 2 years of GLD use prior to cancer diagnosis were included. Linear mixed-effects models were conducted to evaluate changes in HbA_{1c} for colon cancer (CC) and rectal cancer (RC) patients in the 4 years around CRC diagnosis.

Results: Of all CRC patients ($n = 4{,}714$), 294 (6%) GLDs users with CC and 144 (3%) with RC were selected. In the crude model, mean HbA_{1c} at cancer diagnosis was 6.9% (51.6 mmol/mol) among CC patients and 7.1% (53.5 mmol/mol) among RC patients. Among CC patients, HbA_{1c} decreased with 0.12% per year ($p = 0.0002$) before cancer diagnosis in the adjusted model, and after diagnosis, it increased with 0.12% per year ($p = 0.02$). In subgroup analyses, effects on HbA_{1c} were more pronounced in users of anti-anaemic preparations; these preparations are suggested to interfere with HbA_{1c}. Among RC patients, HbA_{1c} decreased before diagnosis with 0.18% per year ($p = 0.0006$), whereas after diagnosis, it changed not significantly.

Conclusions: Among users of GLDs, HbA_{1c} decreased with 0.12–0.18% (1–2 mmol/mol) per year before CRC diagnosis. Only among CC patients, HbA_{1c} increased after diagnosis (0.12% per year; 1.3 mmol/mol). In (un)diagnosed cancer patients, the HbA_{1c} measure to visualise glycaemic control might be influenced by anti-anaemic preparations.

209. Real world treatment pattern trends in patients with multiple myeloma in the US

Xue Song,[1] Ze Cong,[2] Kathleen Wilson.[1] *[1]Truven Health Analytics, Cambridge, MA, USA [2]Onyx Pharmaceuticals Inc, San Francisco, CA, USA [3]Truven Health Analytics, Cambridge, MA, USA*

Background: Over the last decade, several novel agents have been approved in the US for the treatment of patients with multiple myeloma (MM) including proteasome inhibitors (bortezomib and carfilzomib) and immunomudulatory drugs (thalidomide, lenalidomide, and pomalidomide), leading to improved survival of patients.

Objectives: The study aimed to examine the time trends and most recent real-world MM treatment patterns in the US.

Methods: Adult patients newly diagnosed with MM (ICD-9-CM 203.0x) in 1 July 2006 to 31 March 2014 were extracted from MarketScan Databases. Patients were required to have ≥6 months of continuous data prior to (baseline) the first MM diagnosis and were followed until the earliest of inpatient death or end of data. The first three lines of MM treatment regimens and transplant status were identified.

Results: A total of 24 507 MM patients were examined (mean age: 65.2; male: 54.1%; commercial insurance: 52.5%; baseline renal disease: 13.8%; baseline skeletal-related events: 25.6%; mean follow-up: 23 months; transplant: 16.2%). Across all three lines, the proportion of patients on thalidomide-based regimens decreased over time. In first line (1L), bortezomib-based (B, mono or combo) and lenaliomide + bortezomib (L + B)-based regimens became more common from 2006 to 2014 (2006–2007: B, 17.13%; L + B, 2.29%; 2008–Q12014: B, 44.98%; L + B, 17.61%; 2013–Q12014: B, 49.58%; L + B, 23.88%). Patients receiving a transplant were more likely to receive L + B in 1L (35.44%) compared with non-transplant patients (21.77%) in 2013–Q12014. In second line (2L), lenalidomide-based regimens (L) were the most common, followed by B (2013–Q12014: L, 35.13%; B, 23.80%). Combination regimen L + B became more common (2006–2007: 7.93%; 2008–Q12014: 14.26%; 2013–Q12014: 15.58%) in 2L. In third line (3L), carfilzomib- and/or pomalidomide-based regimens were common (32.43%) since 2013 after their FDA approvals.

Conclusions: MM treatment patterns have been dynamic over time, with novel agents becoming established as cornerstones. Combination regimens such as L + B have become more widely used in 1L and 2L. Newly approved agents (carfilzomib and pomaliomide) have become the prevailing treatments in 3L.

210. Pattern of chemotherapy dose delay and dose reduction

Hairong Xu,[1] Chun Chao,[2] Lanfang Xu,[2] Kimberly Cannavale,[2] Olivia Sattayapiwat,[2] John H Page,[1] Roberto Rodriguez,[2] Leila Family.[2] *[1]Amgen, Thousand Oaks, CA, USA [2]Kaiser Permanente Southern California, Pasadena, CA, USA*

Background: Chemotherapy dose delay or dose reduction due to chemotherapy-induced toxicity or other consideration of patient factors has been shown to be associated with worse patient outcomes.

Objectives: The aim was to describe the practice pattern of dose reduction and dose delay in cancer patients in Kaiser Permanente Southern California (KPSC), a large managed care organization.

Methods: Adult patients diagnosed with non-Hodgkin's lymphoma (NHL) and breast, lung, gastric, ovarian, or colorectal cancers from KPSC Health plan (2010-2012) which initiated chemotherapy were included. For each regimen, we estimated the incidences of dose delay (>3-day delay in a given cycle) and dose reduction (>15% decrease relative to standard dose in a given cycle). Incidence proportions of chemotherapy dose delay/reduction were estimated overall and by chemotherapy cycle.

Results: Our study population included 2348 breast cancer, 678 colorectal cancer, 193 gastric cancer, 888 lung cancer, 319 ovarian cancer, and 699 NHL patients. The mean age at diagnosis ranged from 56 years for breast cancer to 67 years for lung cancer. Thirty-seven percent of the study patients ever had a delayed dose in their chemotherapy treatment; 26% percent ever had a dose reduction, and 51% experienced either a dose delay or dose reduction during their chemotherapy. Patients with gastric cancer most commonly experienced chemotherapy dose delay or reduction (78%), whereas patients with breast cancer experienced the least (43%). The proportion of patients who experienced a chemotherapy dose delay or dose reduction increased as the number of cycle advanced, ranging from 20.4% in cycle 2 to 34.5% in cycle 8.

Conclusions: Physicians were found to frequently administer myelosuppressive agents at dose intensities lower than those of standard regimens. The incidences of chemotherapy dose delays and dose reductions varied significantly across tumor types and regimens and were increased with advanced stages and with later cycles.

211. Patterns of antiplatelet use in patients with myocardial infarction and subsequent acute coronary syndrome events

Alfi Yasmina, Anthonius de Boer, Olaf H Klungel, Patrick C Souverein. *Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Utrecht Institute for Pharmaceutical Science, Faculty of Science, Utrecht University, Utrecht, The Netherlands.*

Background: Antiplatelet drugs are important for secondary prevention of cardiovascular events after myocardial infarction (MI).

Objectives: The objectives of this study were to assess the patterns of antiplatelet drug use in patients who had a MI and to evaluate the impact of subsequent acute coronary syndrome (ACS) events on antiplatelet drug use in the Netherlands.

Methods: A descriptive retrospective cohort study was conducted on 4719 patients in Utrecht Cardiovascular Pharmacogenetics studies, who had their first MI during 1986–2009. Medication use was assessed through the Dutch PHARMO Record Linkage System (dispensing database linked to the hospital admission registry). Antiplatelet users were classified as continuous users (gap between consecutive prescriptions ≤90 days), discontinued users (gap of >90 days or no refills), and restarters (with a new antiplatelet drug episode after earlier discontinuation) and were followed for a maximum of 10 years. Antiplatelet drug use in 90 days before and after recurrent consecutive ACS events (MI and unstable angina) following the first MI was also compared.

Results: At 1 year of follow-up, 83.7% patients continued using antiplatelets, 76.9% were still on aspirin, and only 36.4% patients were continuing clopidogrel. Most of the discontinuers restarted antiplatelet drugs later, leading to 74.7% antiplatelet users, 62.1% aspirin users and 35.2% clopidogrel users in 10 years after the index MI. For a subgroup of MI patients who started dual antiplatelet therapy with aspirin and clopidogrel (DAPT) after hospital discharge in 2002–2009, a total of 28.9% remained continuous users in 1 year, whereas 24% of the subjects switched to aspirin or clopidogrel monotherapy. When a recurrent ACS event occurred, antiplatelet use increased by 3.6% ($p < 0.05$) compared with the use after the index MI, with the largest increase was observed for clopidogrel (10.9%, $p < 0.05$).

Conclusions: A significant proportion of MI patients discontinued antiplatelet drugs at 1 year, although they restarted using antiplatelets again later. Clopidogrel was the most common antiplatelet drug to be discontinued after the index MI.

212. Statins prescription rates in a population-based cohort of amyotrophic lateral sclerosis: comparison with the general population

Francesca Palese,[1] Paolo Battiston Giacomelli,[1] Silvia Ussai,[2] Manuela Giangreco,[1] Lorenzo Verriello,[3]

Fabio Barbone,[1,2,4] Giancarlo Logroscino,[5] Federica E Pisa.[1,2] *[1]Department of Biological and Medical Sciences, University of Udine, Udine, Italy [2]Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine, Udine, Italy [3]Department of Neurosciences, Neurologic Clinic, University Hospital of Udine, Udine, Italy [4]Department of Medicine, University of Trieste, Trieste, Italy; [5]Neurodegenerative Diseases Unit, Department of Basic Medicine Neuroscience and Sense Organs, Department of Clinical Research in Neurology, University of Bari, "Pia Fondazione Card G. Panico" Hospital Tricase, Neurodegenerative Diseases, Bari, Italy*

Background: Signals of disproportionally high reporting of amyotrophic lateral sclerosis (ALS) with HMG-CoA-reductase inhibitors (statins) were detected in surveillance databases. A pooled analysis of clinical trials did not find an increased incidence of ALS in the statins arm. Case-control and cohort studies yield inconclusive results. Evidence that statins worsen disease course is also inconclusive.

Objectives: Preliminarily to an analytic study, we assessed statins use in a cohort of ALS patients and in the general population.

Methods: The cohort included all residents of the Friuli Venezia Giulia (FVG) region, Italy, with incident ALS from 2002 to 2009. Cases were identified through multiple sources including health databases; the diagnosis was validated through clinical documentation review. Statins prescriptions in the cohort and in the general FVG population from 2002 to 2009 were obtained from the regional outpatient prescription database, through the ATC classification code C10AA.

We calculated the 2002–2009 annual age–sex-standardized prevalence of statins use, with 95% confidence interval (95%CI). The 2006 census FVG population was the standard.

Results: The cohort included 262 subjects with ALS, 50.4% men, median age at diagnosis 67.4 years. Age–sex-standardized prevalence of statins use was 62.0‰ (95%CI [56.3, 67.6]) in the cohort and 65.2‰ (95%CI [59.6, 70.9]) in the general population.

Fifty-three (20.2%) patients had at least one prescription of a statin in the year before diagnosis, only 16 (6.1%) in the year thereafter.

Conclusions: Prevalence of statin use was similar in ALS cohort and general population. In ALS cohort, the frequency of use decreased after diagnosis. Conflicting study results may have influenced prescribing physicians' and/or patients' decision of discontinue statins.

213. The temporal trend of concomitant prescription of contraindicated drugs in dronedarone users

Chuntao Wu,[1] Andrew Koren,[2] Jane Thammakhoune,[1] Hayet Kechemir,[3] Stephanie Tcherny-Lessenot,[3] Stephen Lin,[1] Juhaeri Juhaeri.[1] *[1]Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, USA [2]Cardiovascular Medical Unit, Sanofi, Bridgewater, NJ, USA [3]Global Pharmacovigilance and Epidemiology, Sanofi, Chilly-Mazarin, France.*

Background: Described in the dronedarone prescribing information and risk evaluation and mitigation strategy communication plan in the US, dronedarone is contraindicated in patients using potent CYP3A4 inhibitors that raise serum concentration of dronedarone and drugs that prolong the QT interval and that may induce Torsade de Pointes.

Objectives: The study aimed to examine the temporal trend of the prevalence of concomitant prescription of potent CYP3A4 inhibitors and QT-prolonging drugs, respectively, in dronedarone users.

Methods: Clinformatics DataMart database was used to identify patients prescribed dronedarone between July 2009 (launch date in the US) and December 2013. The respective prevalence of concomitant prescription for potent CYP3A4 inhibitors and QT-prolonging drugs excluding antiarrhythmics (amiodarone, dofetilide and sotalol), within 30 days before or after initiation or refilling of dronedarone, were calculated for each quarter starting with the third quarter (Q3) of 2009. Such antiarrhythmics were excluded from the analysis on QT-prolonging drugs because concomitant prescriptions of these antiarrhythmics usually indicate switching between such drugs and dronedarone.

Results: A total of 9575 dronedarone users were identified in Clinformatics between July 2009 and December 2013. In this study period, the quarterly prevalence of concomitant prescription for potent CYP3A4 inhibitors was low and stable over time, ranging from 1.0% (95% confidence interval (CI)

[0.5, 1.5] %) in Q1 2010 to 1.9% (95%CI [1.4, 2.5] %) in Q1 2012. The quarterly prevalence of concomitant prescription for potent QT-prolonging drugs excluding antiarrhythmics was also low and stable over time, ranging from 0.9% (95%CI [0.4, 1.3] %) in Q2 2010 to 1.6% (95%CI: 1.0, 2.1] %) in Q1 2013.

Conclusions: The respective quarterly prevalence of concomitant prescription of potent CYP3A4 inhibitors and QT-prolonging drugs excluding antiarrhythmics was low and stable over time in dronedarone users. Therefore, it is reasonable to conclude that the prevalence of actual concomitant use of such drugs has been constantly low since the launch of dronedarone in the US.

214. Impact of new oral anticoagulants (NOACs) on therapy of patients with Japanese patients: descriptive study using commercially available database

Kiyoshi Kubota,[1] Nobuhiro Ooba,[2] Yukari Kamijima,[1] Kuniyasu Sato,[1] Daisuke Koide.[3] *[1]NPO Drug Safety Research Unit Japan, Tokyo, Japan [2]Department of Clinical Pharmacy, Nihon University School of Pharmacy, Chiba, Japan [3]Department of Clinical Epidemiology and Systems, Graduate School of Medicine, University of Tokyo, Tokyo, Japan*

Background: Warfarin and new oral anticoagulants (NOACs) lower the risk of stroke in patients with atrial fibrillation (AF). Therapy with NOACs does not involve frequent dose adjustment. This feature of NOACs may be beneficial in patients with low risk who tend to be untreated.

Objectives: We estimated the impact of NOACs (marketed in 2011) on anticoagulant therapy in Japanese patients with AF using a commercially available database.

Methods: Data of claims between January 2005 and March 2014 were obtained from the Japanese Medical Data Center (JMDC). The enrolment data were also obtained. The standardized prevalence was estimated using the population in 2013 as the standard population. Anticoagulant therapy for AF was defined when the diagnosis code of AF but no other potential indications of anticoagulants preceded the prescription of an anticoagulant. CHADS2 score was estimated in new users who started an anticoagulant after at least a 1-year period of non-use.

Results: The study population (average size, 1.27 million) consisted of 94.5% of young people. A total of 3951 patients receiving anticoagulant therapy for AF were identified. The standardized prevalence of patients with anticoagulant therapy for AF steadily increased from 36.2 (95%CI [30.7, 41.6]) in 2005 to 56.9 [53.1, 60.6] in 2010 and 75.9 [72.0, 79.8] per 100 000 persons in 2013 in young population and 64.5 [37.6, 91.4] in 2005 to 311.6 [272.9, 350.3] in 2010 and 575.6 [528.4, 622.7] per 100 000 in 2013 in old population. In the period 2011–2014, the proportion of patients with CHADS2 score 0 or 1 was 58.6% and 47.2% in young new users of NOAC and warfarin, respectively, with a difference of 11.4 ([5.0, 17.8] %) and 38.7% and 31.9% in old new users of NOAC and warfarin, respectively, with a difference of 6.8 ([−6.0, 19.6] %).

Conclusions: The increase of anticoagulant therapy already took place before the advent of NOACs in accordance with Japanese guidelines for AF treatment issued in 2001 and renewed twice in 2008 and 2013, which encouraged anticoagulant therapy. NOACs may help young patients with relatively low risk have a benefit from anticoagulant therapy.

215. Use of overactive bladder medications in the adult population of the UK: a cohort study in the Clinical Practice Research Datalink

Andrea V Margulis,[1] Lisa J McQuay,[2] Susana Perez-Gutthann,[1] James A Kaye,[3] Alejandro Arana.[1] *[1]Epidemiology, RTI Health Solutions, Barcelona, Spain [2]Epidemiology, RTI Health Solutions, Research Triangle Park, NC, USA [3]Epidemiology, RTI Health Solutions, Waltham, MA, USA*

Background: Within a program exploring the safety of antimuscarinic drugs used to treat overactive bladder, we describe the use of these drugs.

Objectives: The aim was to characterize users and the use of darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium.

Methods: We followed all persons aged ≥18 years with no cancer or HIV and with a prescription for a study drug and no prescriptions for the same drug in the previous year until a cancer outcome, death, disenrollment, or end of the study period (2004–2012). We created therapy episodes by concatenating prescriptions, allowing gaps ≤60 days. Reasons for ending therapy episodes were drug not refilled, drug

added (add-on), or drug switch. We provide descriptive results.

Results: The study cohort had 119 913 persons (70% women, mean age at cohort entry 62 years, mean follow-up 3.3 years); 51% were ever smokers (16% current, missing data 1%); 52% had low/moderate alcohol intake and 18% high (6% unknown amount, missing data 10%). At cohort entry, 81% of subjects had hypertension, 11% diabetes, 13% coronary heart disease, and 3% heart failure.

Most subjects entered the cohort with prescriptions for oxybutynin (34%), tolterodine (31%), or solifenacin (28%); fewer were on darifenacin, fesoterodine, or trospium. Index therapy episodes were shortest for oxybutynin (mean [SD], 5.5 [10.9] months) and longest for darifenacin (8.9 [14.4] months); 53–60% of oxybutynin, solifenacin, and tolterodine index therapy episodes lasted 1–3 months; 15–22% continued beyond 9 months.

Of the study subjects, 73% were exposed to a single drug during a follow-up. There were 245 833 therapy episodes (28% oxybutynin, 27% solifenacin, 26% tolterodine, and 10% polytherapy). There was no dose change in 88% of the therapy episodes. Drugs were not refilled in 89–92% of oxybutynin, solifenacin, or tolterodine episodes; there were add-ons in 8–11% of the same and a few switches. Solifenacin was the most common drug added or switched to.

Conclusions: This cohort of OAB drug users comprised mostly elderly females using one drug during a follow-up. The observed exposure patterns are well suited to detecting acute adverse events for individual OAB drugs.

216. Use of oral non-steroidal anti-inflammatory drugs in people with asthma

Daniel R Morales,[1] Peter T Donnan,[2] Bruce Guthrie.[1]
[1]Medical Research Institute, University of Dundee, Dundee, UK [2]Dundee Epidemiology and Biostatistics Unit, University of Dundee, Dundee, UK

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) trigger exacerbations in susceptible people with asthma. Risk from NSAID-induced asthma exacerbations varies according to selectivity for the cyclooxygenase-2 enzyme (COX2), with COX2 inhibitors appearing to have the safest profile.

Objectives: The objective of the study was to measure oral NSAID prescribing trends in people with asthma in a UK primary care population.

Methods: Data from UK Clinical Practice Research Datalink was used to form a cohort of people with active asthma in which the quarterly prevalence of oral NSAID prescribing was measured between 2000 and 2012. Active asthma was defined by the presence of Read codes and use of asthma medication. Oral NSAIDs were grouped into one of four categories: COX-2 inhibitors, NSAIDs with 5–50-fold COX-2 selectivity, NSAIDs with <5-fold COX-2 selectivity, and non-selective NSAIDs. NSAID prescribing trends were plotted, and relative changes in the prevalence of NSAID prescribing over the study period were calculated with 95% confidence intervals (95%CIs).

Results: The cohort included 281 954 people with active asthma. A total of 77 424 patients in the active asthma cohort (27.5%, 95%CI [27.3, 27.6]) were prescribed an oral NSAID in primary care. Of these, the most commonly prescribed NSAIDs were as follows: NSAIDs with <5-fold COX2 selectivity (44%), non-selective NSAIDs (35%), COX2 inhibitors (12%) and NSAIDs with 5–50-fold COX2 selectivity (8%). Oral NSAID prescribing varied significantly by age and gender. Prescribing of non-selective NSAIDs and NSAIDs with <5-fold COX2 selectivity rose and fell by 37%, respectively, over the 12-year period, largely driven by changes in diclofenac and naproxen prescribing. There was a rise and rapid fall in COX2 inhibitor prescribing in 2004 associated with the timing of NSAID cardiovascular safety concerns.

Conclusions: There have been significant changes in oral NSAID prescribing trends in UK primary care between 2000 and 2012, probably driven by cardiovascular safety concerns. COX2 inhibitors are infrequently prescribed to people with asthma despite their apparent safety profile in people with NSAID-sensitive asthma.

217. Use of antipsychotics (AP) in mental health secondary care setting vs primary care

Deborah Layton,[1,2] Vicki Osborne,[1,2] Miranda Davies,[1,2] Ian Ratcliffe,[1] Sarah Clarke,[1] Saad AW Shakir,[1,2] Joe Reilly,[3] Tony Hale.[4] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK [3]Centre for Integrated Health Care Research, Durham University, Stockton on Tees, County Durham, UK [4]University of Kent, Canturbury, Kent, UK*

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Background: Safety studies conducted exclusively in the primary care setting may be subject to bias because of exclusion of patients (pts) who are managed predominantly within secondary care. These pts may have different characteristics and health events to those treated in primary care for similar indications. The risk management plan for quetiapine extended release (Seroquel XL©) had a need to describe utilisation and monitor safety as prescribed in primary care (in a modified prescription-event monitoring (MPEM) – all indications) and in mental health secondary care (in a specialist cohort event monitoring (SCEM) – ENCePP study reg.5412 – schizophrenia (Schiz) and bipolar disorder (BD) indications only).

Objectives: An *ad hoc* analysis aimed to describe the characteristics of two study cohorts prescribed Seroquel XL© for similar indications under normal conditions of use in each setting.

Methods: Exposure, selected past medical history (pmh) and prior medications use (including quetiapine immediate release (IR)) data were collected from forms sent to specialists December 2009–December 2012 and to General Practitioners (GPs) September 2008–February 2013. Descriptive statistics and univariate analyses were performed (% denominator assumes no missing data).

Results: The SCEM cohort (869) included 258 pts (40%) with Schiz and 345 pts (53%) with BD. The MPEM cohort (13 276) included 2373 pts (18%) with Schiz and 3820 pts (30%) with BD. In those with Schiz, SCEM pts were more likely than MPEM pts to be <30 years old, have a pmh of depression, extrapyramidal symptoms (EPS) and prior antipsychotic (AP) use, but prior IR use was less likely. In those with BD, SCEM pts were more likely than MPEM pts to have a pmh of depression, EPS, diabetes and AP use, and prior IR use was less likely.

Conclusions: In this *ad hoc* analysis, SCEM pts appeared overall to have a higher burden of some pre-existing conditions (depression, EPS and diabetes) than MPEM pts, highlighting important differences in pt risk profiles. Considerations include differences in the recording of data in medical records held by specialists vs GPs. Nevertheless, these findings support the need for systematic surveillance across both primary and secondary care settings to avoid exclusion of high risk pts.

218. Sex difference in antidepressant use in brain injury rehabilitation centres

Veronica Campagnol,[1] Silvia Ussai,[2] Giorgia Cosano,[1] Manuela Giangreco,[1] Tullio Giorgini,[3] Emanuele Biasutti,[3] Fabio Barbone,[1,2,4] Federica E Pisa.[1,2] *[1]Department of Biological and Medical Sciences, University of Udine, Udine, Italy [2]Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine, Udine, Italy [3]Unit for the Rehabilitation of Acquired Neuropsychological Disturbances, Institute of Rehabilitation and Physical Medicine Gervasutta Hospital, Udine, Italy [4]Department of Medicine, University of Trieste, Trieste, Italy*

Background: Depression is common after acquired brain injury (ABI), affecting up to 50% of patients. A multidisciplinary therapeutic approach, including antidepressants, is recommended.

Objectives: This 1-day survey investigated the use of antidepressants (ATDs) in patients with ABI hospitalized in in tertiary rehabilitation centres in Italy.

Methods: Centres were identified through the roster of the society for rehabilitation medicine. All the inpatients with ABI, following a traumatic or non-traumatic cause, at the day of the survey were included. For each patient, the treating physician compiled a structured questionnaire, inquiring on gender, age, Rancho Level of Cognitive Functioning Scale (LCF) score at admission and time (weeks) since ABI occurrence. The medications used on a single day (the day before the survey) were extracted from the anonymized medication chart. Odds ratio (OR), with 95% confidence interval (95%CI), of ATDs use was calculated through unconditional logistic regression.

Results: Out of the 484 enrolled patients, 55.6% aged 35–64 years and 63.4% were men; 155 (32.1%) used ATDs. The prevalence of use was higher in women (41.2%) vs. men (27.0%). SSRIs were the most used ATDs, by 67.1% of users, followed by other ATDs (38.1%) and MRIs (6.5%). When simultaneously adjusting for age, LCF score and time since ABI, women were more likely to use antidepressant (OR = 1.8; 95%CI [1.2, 2.7]) than men.

Conclusions: About one-third of patients used ATDs. SSRIs were the most used ATDs, consistently with guidelines and previous surveys. Women were 80% more likely to use ATDs than men. This finding may indicate that depression post-ABI is more frequent in

women or reflect the sex difference in pre-ABI prevalence of depression.

219. Trends in prescribing patterns for cabergoline in 4 European countries

Cynthia de Luise,[1] René Schade,[2] Gianluca Trifirò,[2,3] Lars Pederson,[4] Ron Herings,[5] Miriam Sturkenboom.[2] *[1]Department of Epidemiology, Pfizer, New York, NY, USA [2]Department of Informatics and Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands [3]Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Messina, Italy [4]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark [5]PHARMO Institute for Drug Outcome Research, Utrecht, The Netherlands*

Background: In 2008, several revisions to the summary of product characteristics (SPC) were implemented for cabergoline concerning second-line use and maximum daily dose (MDD) for Parkinson's disease and the need for baseline and serial echocardiographic monitoring. Earlier warnings occurred in 2007. The effect of labelling changes and warnings on prescribing patterns for cabergoline is noteworthy.

Objectives: The study aimed to describe prescribing patterns of cabergoline over a 5-year period for prolactin reduction indication (PRI) and neurological indication (NI), in 5 databases in 4 European countries.

Methods: We conducted a multi-country retrospective cohort study using five electronic healthcare databases in four European countries: The Health Information Network (THIN)-UK, Health Search/CSD Patient Database (HSD)-IT, PHARMO-NL, Integrated Primary Care Information (IPCI)-NL and Aarhus-DK, representing a combined population of >10-million persons. All persons with prescription(s) for cabergoline between 1 January 2006 and 30 June 2012 were divided into new and prevalent users. Incidence and prevalence rates of use per 1000 person-years (py) by ATC codes, frequency of doses >3 mg per day for PRI and NI and second-line prescriptions for NI were calculated.

Results: A total of 21 953 users of cabergoline were identified. Mean age was 40.8 years for PRI and 70.4 years for NI. In all databases, incidence and prevalence of use were higher for PRI than for NI. Except for PRI in Aarhus, incidence and prevalence of usage of cabergoline declined steadily over time for PRI and NI. The largest reduction in incidence of use was for NI in HSD from 0.23 to 0.01 (females) and from 0.13 to 0.02 (males) per 1000 py, respectively, between 2006 and 2011. Dosages >3 mg per day declined from 6% to 1% of total prescriptions (PRI and NI) between 2006 and 2011. While there was evidence of first-line use for NI, this steadily declined over the years studied.

Conclusions: Between 2006 and 2011, there was a reduction in overall use of cabergoline in four EU countries for both PRI and NI (except for PRI in Aarhus), and dosages rarely exceeded the MDD of 3 mg. While there was evidence of first-line use of cabergoline for NI, this became less frequent over the years studied.

220. Drug utilization (DU) study of Seroquel® extended release (XR) prescribed by psychiatrists as treatment for major depressive disorder (MDD) in selected countries in the European union (EU)

Robert S Brody,[1] Charlie L Liss,[1] Wray Heather,[2] Anneli Thurreson,[2] Leigh Jefferies.[3] *[1]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA [2]AstraZeneca R&D, Mölndal, Sweden [3]AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA*

Background: A DU study in five EU countries was performed as a condition of market authorization for the new MDD indication for Seroquel® XR.

Objectives: The objectives were to document the characteristics of patients (pts) under psychiatric care who were prescribed Seroquel® XR for MDD in five European countries (SE, DE, IT, RO, and ES) and to describe the differences in treatment practices in the countries.

Methods: This study evaluated antidepressant (AD) DU for treatment of major depressive episodes associated with MDD following the launch of Seroquel® XR. Data were abstracted from psychiatrists' medical records and included physician input on key variables. Descriptive statistics were used to characterize physician and pt characteristics and DU. Multivariate modeling was used to define variables predictive of dosing above the recommendations in the SmPC and treatment pattern as monotherapy (off-label).

Results: Pts' psychiatric histories were similar across countries and indicated a burden of severe MDD. Demographic characteristics of pts were similar across countries except for an 8-year younger mean age at treatment in SE. Physicians' ratings of the therapeutic effect of prior treatment with AD in categories of "minimal or slight improvement" or "unchanged or worse" suggested the need for add-on AD treatment for the majority of pts in each country, except DE; 15.7% of patients initiated treatment with Seroquel® XR as monotherapy. Aside from this finding, similarities in DU were observed and found to be largely in accordance with the recommendations in the SmPC, although initial and maintenance doses were observed to be higher than the recommended limits in a small proportion of pts; this proportion differed across countries. Modeling of predictive factors for higher than the recommended doses identified psychosis as a predictor.

Conclusions: The information from this study, together with other PASS, indicates that Seroquel® XR is being prescribed for MDD at doses that are similar in pts across Europe. Some differences in demographics and treatment patterns were seen between Sweden and other countries.

221. Risk of injury with sedative hypnotic use in an over-65 population

Sanket Shah, Julieta Scalo, Karen Rascati. *Division of Health Outcomes and Pharmacy Practice, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA*

Background: The American Geriatric Society cautions against the use of benzodiazepines (BZDs) and, chronically, benzodiazepine receptor agonists (BzRAs) in people aged 65 years or older. Sedation from these hypnotics can persist into waking hours, potentially increasing the risk of injury. With a shorter half-life and milder sedative effects, melatonin receptor agonist ramelteon may be a suitable alternative hypnotic, but evidence about its use in older populations is limited.

Objectives: The primary objective was to investigate the association between hypnotic use and risk of injury. The secondary objective was to compare the risk of injury between benzodiazepines, BzRAs, and ramelteon.

Methods: This was a retrospective case-control study of adults 65 years or older enrolled in Medicare Advantage plans of a large commercial insurer. Cases were defined as anyone with a coded diagnosis (International Classification of Diseases-9) of injury resulting in hospital or emergency department admission between 1 January 2008 and 31 December 2010, and hypnotic exposure, stratified by drug class, was evaluated within 90 days of the index date. Hypnotic exposure for eligible controls was evaluated in a continuous 3-month period. Further analysis will include controls matched on demographic characteristics, logistic regression with covariates, and odds ratios.

Results: From a base population of about five-million Medicare patients 65 and over who met study criteria, we identified 157 839 eligible cases of injury. Of these, 20 193 (12.79%) used a hypnotic within 90 days of the index date: 11 842 (7.50%) used BZDs, 8306 (5.26%) used BzRAs, and 45 (0.03%) used ramelteon. Among the eligible controls, we identified 235 084 (4.81%) hypnotic users in a continuous 3-month period: 108 547 (2.22%) used BZDs, 116 290 (2.38%) used BzRAs, 9744 (0.19%) used a combination of BZD/BZRAs, and 1156 (0.02%) used ramelteon.

Conclusions: Over the age of 65 years, hypnotic use, and especially the use of BZDs, appears to be more common among those admitted to hospitals and emergency departments with injuries. The economic consequences of injuries warrant further study of the comparative safety of ramelteon.

222. National trends in adult bipolar disorder subtypes and prescribed psychotropic medications

Thiyagu Rajakannan,[1] Dinci Pennap,[1] Daniel J Safer,[2] Julie M Zito.[1] *[1]Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD, USA [2]Department of Psychiatry and Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA*

Background: The diagnosis of adult bipolar disorder has increased dramatically in community practice in the past two decades. Little is known of recent trends in the diagnosis of adult bipolar disorder subtypes and of associated psychotropic medication use in this population.

Objectives: The study aimed to report the national trends in adult bipolar disorder subtypes (Bipolar-I/II/NOS) between 1999 and 2010 and in related

psychotropic medications prescribed during outpatient physician office visits.

Methods: A cross-sectional study design was applied to the National Ambulatory Medical Care Survey data (NAMCS) linked with the National Hospital Ambulatory Medical Care Survey data (NHAMCS) for the calendar years 1999–2010 in combined 4-year intervals. Physician office visits for bipolar disorder in adults (aged 18–64) were categorized as meeting full diagnostic criteria (FC) or subthreshold criteria (NOS, not otherwise specified) using ICD 9-CM codes. Using population weighted Chi-square and logistic regression analyses; we assessed trends for FC and subthreshold diagnoses and compared prescribed psychotropic medication use between bipolar FC and subthreshold visits.

Results: Physician office-based adult bipolar visits increased from 6.8% in 1999–2002 to 11.4% in 2007–2010 ($\chi 2 = 30.5$; df = 2; $p < 0.0001$). Over the 12-year study period, significant increases occurred in bipolar NOS diagnoses (3.6–55.6%), whereas bipolar-I diagnoses decreased from 87.0% to 29.1% ($\chi 2 = 173.9$; df = 2; $p < 0.0001$). Psychotropic medications prescribed during office visits increased over time for both FC and NOS diagnoses; notably, antipsychotics were increased ($p = 0.02$), and lithium was decreased ($p = 0.03$). By 2007–2010, prescribed antipsychotics alone and with other psychotropic medications were comparable for FC and NOS diagnoses.

Conclusions: Between 1999 and 2010, bipolar NOS diagnoses in adults increased 15-fold and became a predominant bipolar subtype. Prescribed psychotropic medications became proportionally similar by 2007–2010 in bipolar FC and NOS.

223. Patterns of prescription refill and pregabalin: a 5-year prospective cohort study on high consumption

Micaela Tjäderborn,[1] Carola Bardage,[2] Staffan Hägg,[1,3] Elisabet Nikolic,[4] Anna K Jönsson.[5]
[1]Division of Drug Research, Department of Medicine and Health, Linköping University, Linköping, Sweden [2]Department of Rational Use of Medicines, Medical Products Agency, Uppsala, Sweden [3]Academy for Health and Care, Region Jönköping County, Jönköping, Sweden [4]Department of Medical and Health Sciences, Linköping University, Linköping, Sweden [5]Department of Clinical Pharmacology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden

Background: Pregabalin is a widely used anticonvulsant, analgesic and anxiolytic prescription drug for which euphoria, tolerance, withdrawal, dependence, drug abuse and fatal intoxications have been reported. Drug diversion occurs, but the prevalence is unknown.

Objectives: The aims of the study were to describe pregabalin refill patterns and sub-groups of patients with a focus on high consumption and to follow changes in refill patterns during 5 years for patients starting new treatment.

Methods: The study included subjects who refilled a prescription of pregabalin (ATC N03AX16) in Sweden 1 January 2007 to 31 December2008. Dispenses of pregabalin during 5 years were followed. Descriptive statistics were used to characterize the population. Lorenz curves described the distribution of drug dispenses in the population. High consumers were defined as subjects with a daily dose of >600 mg, any consecutive 6 months during the study. Incident users were defined as subjects with no pregabalin dispense within 12 months preceding the study. Logistic regression adjusting for co-factors will be used to identify the differences between high consumers and others. Dispenses for incident users will be analyzed using time-series analysis and Kaplan–Meier survival analysis. Main outcome variables include change in daily dose from first to last year. Sensitivity analyses will test the chosen cut-offs. p-values > 0.05 are considered significant.

Results: A total of 54.544 individuals were identified, of which 61% were women, 87% were incident users and the median age (range) was 54 (5–103) years. A total of 677.734 pregabalin dispenses were registered. In 23.9% of individuals, only one dispense was registered, and the median number of dispenses(range) was 4 (1–347). Lorenz curves, regression analyses, time-series analyses and survival analyses will further investigate refill patterns in these subjects.

Conclusions: Epidemiological data on prescription refill patterns may assist in investigating whether high consumption of prescriped pregabalin occurs. Preliminary data for the present population indicate that the drug is dispensed by a sub-group of the patients in amounts that are well above the dosing recommendations for this drug.

224. Use of varenicline in a Canadian province: a population-based study

Noor Breik,[1] Shelley Derksen,[2] Silvia Alessi-Severini.[1] *[1]Faculty of Health Sciences, College of Pharmacy, University of Manitoba, Winnipeg, MB, Canada [2]Manitoba Centre for Health Policy, University of Manitoba, Winnipeg, MB, Canada*

Background: Varenicline (Champix), a prescription medication specifically indicated for smoking cessation, has been available on the Canadian market since 2007. Historically, provincial drug plans in Canada have not reimbursed products categorized as 'lifestyle' medications, but policies have recently changed to address high smoking rates. This study reports on the utilization of varenicline in the entire population of a Canadian province with a universal health care system and a publicly funded insurance for prescription drugs.

Objectives: The aim was to describe the population of users of varenicline in the Canadian province of Manitoba.

Methods: Administrative health databases from the Population Health Research Data Repository at Manitoba Centre for Health Policy (MCHP) were accessed to determine incident use of varenicline in the entire population of Manitoba (2007–2012). The cohort of incident users was stratified by sex, age subgroup, area of residence and income quintile. Previous use of bupropion, also indicated for smoking cessation, was determined. Diagnoses of cardiovascular, cerebrovascular, respiratory tract diseases and mental illness were identified using ICD-9-CM and ICD-10-CM codes in medical and hospital files. Analyses were conducted with SAS® statistical software.

Results: A total of 36 896 persons were started on varenicline between 2007 and 2012: 50% were males, 68% were between 35 and 65 years of age and 44% lived in rural areas. In 2007/2008, 65% belonged to the high-income brackets compared with 55% in 2011/2012. Previous use of bupropion was recorded in approximately 13% of varenicline users. Approximately 31% had a diagnosis of cardiovascular or cerebrovascular disease, and 21% had a diagnosis of asthma or COPD. Depression was present in 44% of the cohort of varenicline users.

Conclusions: It is important to define the characteristics of smokers needing prescription medications. Programs and policies should aim at reaching indigent and disadvantaged populations.

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225. Psychopharmacological treatment patterns in bipolar disorder – a nationwide register-based study

Louise Bjørklund,[1,2] Henriette Thisted,[3] Ole Mors,[1,2,4] Søren D Østergaard,[1,2] Christiane Gasse.[3] *[1]Department P, Aarhus University Hospital, Risskov, Denmark [2]The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark [3]National Centre for Register-based Research, Aarhus University, Denmark [4]Centre for Integrated Register-based Research at Aarhus University (CIRRAU), Denmark*

Background: In bipolar disorder, antidepressant treatment without mood stabilizers (antidepressant monotherapy) is associated with the development of mania and rapid cycling and is therefore not recommended.

Objectives: The study aimed to investigate the psychopharmacological treatment patterns in bipolar disorder with a focus on antidepressant monotherapy.

Methods: This is a cohort study with annual cross-sectional assessment of psychotropic drug use between 1997 and 2012 for all Danish residents aged 10 years or older with a diagnosis of bipolar disorder registered in Danish Psychiatric Central Research Register since 1969. Prevalent users of psychotropic drugs were defined as individuals having filled at least one prescription for a psychotropic drug in the relevant year.

Results: We identified 20 618 individuals between 1997 and 2012 with a diagnosis of bipolar disorder. The incidence rate of bipolar disorder doubled over the study period, and the mean age at first diagnosis decreased from 54 years in 1997 to 41 years in 2012. The prevalence of antidepressant use increased from 45% in 1997 to 52% in 2012 with the prevalence of tricyclic antidepressant use decreasing from 17% to 8%. There was an increase in the use of atypical antipsychotics and antiepileptic drugs especially for lamotrigine and valproate. Conversely, there was a decrease in lithium and typical antipsychotic prescriptions. The proportion of

patients treated with antidepressant monotherapy remained unchanged at approximately 20% over the study period.

Conclusions: The results suggest a trend towards more individuals being diagnosed with bipolar disorder, earlier diagnosis of bipolar disorder, and more frequent use of antiepileptics and less use of lithium in the treatment of bipolar disorder. Notably, the prevalence of antidepressant monotherapy remained unchanged over the study period in spite of increased warnings against its use. These findings warrant further investigation.

226. Pattern mining of drug prescriptions suggests complications from chronic opioid use

Yen Low,[1] Tanya Podchiyska,[1] Nigam Shah,[1] Anna Lembke.[2] *[1]Stanford Center for Biomedical Informatics Research, Stanford University, Stanford, CA, USA [2]Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA*

Background: Emerging data suggest that chronic (>90 days) opioid therapy is associated with adverse medical effects, including but not limited to increased pain, suppressed respiration, immunosuppression, and constipation. Furthermore, opioids are implicated in increasing overdose fatalities, most often when used in combination with benzodiazepines.

Objectives: The objective of the study was to examine the commonly observed sequential patterns of drugs prescribed after initiation of chronic opioid therapy as possible markers of opioid-induced side effects.

Methods: Using Stanford Hospital's electronic health records, we identified incident users of opioids (18 years old and above) who had a minimum washout period of 90 days before opioid initiation, were started on at least 90 days of opioids or received a repeat opioid prescription within 90 days, and were subsequently followed for at least 1 year. Their prescriptions 3 months before and at least 1 year after opioid initiation were normalized to generic ingredients by RxNORM, mapped to Anatomical Therapeutic Classification drug classes and examined by sequential pattern mining, which identified common drug sequences by frequency. We restricted items to 24 drugs and drug classes for computational feasibility.

Results: We identified 8879 incident users of chronic opioid therapy. Opioids were often prescribed concurrently with other non-opioid analgesics (72%), antiemetics (62%), and benzodiazepines (37%). After starting opioids, 67% of patients received another non-opioid analgesic, 55% a respiratory drug, 46% an antibiotic, 45% a cardiac drug, 28% a corticosteroid, 26% naloxone or other opioid antagonist, and 23% an anti-constipation drug.

Conclusions: The high rate of opioid and benzodiazepine co-prescribing (37%), along with the finding that a quarter of patients required an opioid antagonist subsequent to initiating opioid therapy, suggests that a high number of patients are at risk for opioid-related overdose. Although the medications prescribed after opioids may represent progression of underlying comorbidities, they may also be markers for the occurrence of opioid-induced side effects.

227. Prescribing patterns of proton pump inhibitors in patients with NSAID use – a comparison between switzerland and the UK in primary care

Fabienne AM Biétry,[1,2] Oliver Reich,[3] Susan S Jick,[4] Christoph R Meier.[1,2,4] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland [3]Department of Health Sciences, Helsana Insurance Group, Zürich, Switzerland [4]Boston Collaborative Drug Surveillance Program, Boston University, Lexington, MA, USA*

Background: Proton pump inhibitors (PPIs) are effective in reducing the risk of gastro-duodenal bleeding caused by non-steroidal anti-inflammatory drugs (NSAIDs) and have become more and more popular over time. There are no studies describing the PPI prescribing patterns in the Swiss ambulatory setting.

Objectives: The aim was to examine the frequency of concurrent prescribing of PPIs and NSAIDs (on the same day and within ±90 days of an NSAID prescription) in Switzerland and the UK. We further aimed at assessing co-prescribing of PPIs in individuals with co-medication of NSAIDs plus systemic steroids or plus anticoagulants.

Methods: We conducted a descriptive study on the health resource utilization by using claims dataset from the large Swiss Health Insurance Helsana and data from the Clinical Practice Research Datalink (CPRD). We included all patients who received at

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least one prescription of an NSAID between 2010 and 2013. They must not have received another NSAID prescription in the previous 180 days. We focussed on the first-time NSAIDs prescription during the study period for this analysis.

Results: In Switzerland, 17.5% of all 645 158 patients with a first-time NSAID prescription were identified to have a concurrent prescription of a PPI on the same day (31.8% within ±90 days). The concurrent prescribing of PPIs in patients with NSAIDs plus systemic steroids on the same day was lower (16.4%) but higher in patients with NSAIDs plus anticoagulants (33.0%) (45.5% vs. 52.6% within ±90 days, respectively). In the UK, 18.9% of 981 938 patients with a first-time NSAID prescription were identified to have a concurrent PPI prescription on the same day (30.1% within ±90 days). Significantly higher prescribing rates of PPIs were observed in patients with a co-medication of NSAIDs plus systemic steroids (35.5%) or plus anticoagulants (46.4%) on the same day (52.2% vs. 60.7% within ±90 days, respectively).

Conclusions: The frequency of co-prescribing of PPIs in patients with NSAIDs plus systemic steroids or anticoagulants was significantly higher in the UK. In the absence of such concurrent drug use, the differences between the two countries were small.

228. Determining exposure of newly initiated antipsychotic medication in a cohort of elderly dementia patients

Kimberly A Fernandes,[1] Mina Tadrous,[1] Diana Martins,[1] Zhan Yao,[1] Samantha Singh,[1] Nathan Herrmann,[2] Muhammed Mamdani,[1] David Juurrlink,[1] Tara Gomes.[1] *[1]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada [2]Division of Geriatric Psychiatry, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Antipsychotics are used to manage symptoms of dementia in the elderly, and considerable research has been dedicated to describing its potentially inappropriate use. However, antipsychotic prescribing in this population comprises a number of diverse medications with varied administration routes, indications, and dosing. This treatment diversity poses a challenge to understanding the actual antipsychotic exposure in these patients.

Objectives: This study aims to develop a method to capture all types of antipsychotic prescribing using an equivalent dosing measure and apply this method to report on the patterns of use among elderly dementia patients in Ontario.

Methods: Using Ontario Drug Benefit claims, treatment patterns were summarized in a population-based cohort of dementia patients aged 66 years and above who newly initiated antipsychotic therapy between 2009 and 2012. Index dose was summarized by adding the equivalent daily dose (eDD) for all antipsychotics prescribed on the initiation date, where each eDD was calculated by multiplying the daily dose by the chlorpromazine dose equivalent. To yield accurate doses, we used recommended prescribing intervals and drug unit costs to impute the quantity and days' supply values for injectable and oral-liquid therapies. Results were summarized by living status and drug class at therapy initiation.

Results: A total of 45 444 continuous users of antipsychotics initiated therapy from 2009 to 2012; 89% of whom initiated atypical therapy. Prior to data cleaning, the index eDDs ranged from 0.4–1 785 000 mg, after the index eDDs ranged from 1–5000 mg. The median initial dose was 40 mg for atypical users in both the community and LTC and was 3–4 times higher for typical users (community 120 mg; LTC 172 mg). The median dose after 1 year doubled from initiation for atypical users (community 75 mg; LTC 80 mg). In contrast, the median dose for typical users decreased in both the community and LTC (80 and 100 mg, respectively).

Conclusions: Diverse antipsychotic prescribing regimens can be compared by calculating an equivalent daily dosage. Future studies should consider incorporating this methodology when describing antipsychotic burden in the elderly.

229. Drug switches in antiretroviral regimens: results of a 5-year historical cohort

Cristiane A Menezes de Pádua,[1] Letícia P Braga,[1] Débora C Hilário,[1] Míriam M Lima Souza,[1] Lorenza N Campos Dezanet.[2] *[1]Departamento de Farmácia Social, Faculdade de Farmácia, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil [2]FHEMIG - Hospital Eduardo de Menezes, Belo Horizonte, MG, Brazil*

Background: The increase of antiretroviral (ART) switches could trigger cross-resistance between drugs from the same therapeutic class. It could lead to therapeutic failure, which brings the necessity of salvage therapy.

Objectives: The study aimed to estimate the frequency of drug substitution of the first-line ART regimen in a 5-year cohort study and describe the reasons for switching.

Methods: This is a historical cohort study carried out with treatment naive HIV-infected adult patients ($n=247$) initiating ART between 2001 and 2005 from three public HIV/AIDS reference centres in Belo Horizonte, Brazil. These patients were followed up for 5 years, and their medical charts were reviewed after the first ART prescription. Descriptive analysis was performed to estimate the incidence of drug switching in ART and to describe the reasons for ART substitution. Kaplan–Meier plots were used to describe the probability of ART switching due to any reason and to estimate the median time free of drug substitution.

Results: One-hundred forty eight (60.32%) were male, and the median age was 36.8 years (95%CI [35.5, 38.0]). Over a median follow-up of 35 ± 1 month, 115 (47.7%) out of 241 patients eligible for Kaplan–Meier analysis switched ART at least once. The incidence rate of drug switch was 1.36 switches/100 persons-month. The most frequent therapeutic regimen switched was 2NRTIs + PI-based regimen (40%), followed by 2NRTIs + 1NNRTIs-based regimen (31.3%). The median survival time free of drug switch was 54 months. The cumulative probability of ART substitution at 12, 24, 36, 48 and 60 months was 21.1%, 30.7%, 39.9%, 47.7% and 51.8%, respectively. Reasons for switching were recorded for 85 (73.9%) patients, 40 (34.8%) owing to adverse reactions to ART, 17 (14.8%) to therapeutic failure and 11 (9.6%) to non-adherence.

Conclusions: ART substitution occurred mostly at the first 12 months of follow-up, mainly due to adverse drug reactions. It requires the necessity of adequate monitoring of ART regimens at the beginning of the treatment of HIV/AIDS patients.

230. Dose and duration of use among commercially insured adults prescribed immediate-release (IR) or extended-release (ER) oxycodone

Angela DeVeaugh-Geiss, Paul Coplan, Aditi Kadakia. *Purdue Pharma LP, Stamford, CT, USA*

Background: One study has described a higher fatality rate for 30-mg IR vs. ER oxycodone (69 vs. 23 deaths/100 000 prescriptions) and for 30-mg IR vs. 80-mg ER oxycodone (69 vs. 25 deaths/100 000 prescriptions). However, the utilization of IR oxycodone, including long-term treatment at higher doses, has not been described.

Objectives: The aim was to examine the utilization of IR and ER oxycodone for the treatment of chronic pain, particularly at higher doses.

Methods: Using a national commercial insurance database (MarketScan; January 2008 to September 2013), patients ≥18 years old with a new IR oxycodone combination, IR oxycodone single-entity (SE), or ER oxycodone prescription and 18 months insurance enrollment (6 months before and 12 months after index prescription) were identified. The primary outcomes were the number of new users in each sample who were prescribed long-term treatment (>90-day continuous use with no gaps in supply ≥15 days) and the average morphine equivalent dose in the fourth month of treatment (conversion, 1.5:1 oxycodone:morphine).

Results: In the MarketScan Commercial database covering 113-million insured individuals between January 2008 and September 2013, there were 2 280 196 IR oxycodone combination users, 269 613 IR oxycodone SE users, and 121 289 ER oxycodone users who met the study inclusion criteria. Only a small proportion of patients met the criteria for long-term (>90 days) treatment with IR oxycodone combination (1.9%), or IR oxycodone SE (11.9%), as compared with a larger proportion of ER oxycodone patients (22.2%). However, the number of patients prescribed long-term IR oxycodone combination ($n=43\,816$) or IR oxycodone SE ($n=32\,184$) exceeded that for ER oxycodone (26 946). At month 4, <5% of patients on IR oxycodone combination received doses >100 mg/d ($n=2127$). In contrast, 39% of patients on IR oxycodone SE ($n=12\,532$) were prescribed doses >100 mg/d, and the number of patients on >100 mg/d IR oxycodone SE exceeded the number of patients on >100 mg/d ER oxycodone (39%, $n=10\,495$).

Conclusions: IR oxycodone is commonly used to treat chronic pain at higher opioid doses (>100 mg), predominantly IR oxycodone.

231. Medicare Part D's impact on pain management in dual-eligible nursing home residents with cancer: an interrupted time-series study

Camilla B Pimentel,[1] Kate L Lapane,[2] Allison B Rosen,[2] Jerry H Gurwitz,[3] Becky A Briesacher.[4] *[1]Clinical and Population Health Research Program, Graduate School of Biomedical Sciences, University of Massachusetts Medical School, Worcester, MA, USA [2]Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA [3]Meyers Primary Care Institute, Worcester, MA, USA [4]Department of Pharmacy Practice, School of Pharmacy, Bouvé College of Health Sciences, Northeastern University, Boston, MA, USA*

Background: Fentanyl patches are commonly employed to treat nursing home (NH) residents with intractable cancer pain. However, access to fentanyl patches—among the strongest and most expensive of opioid formulations—may have been affected by coverage restrictions of Medicare Part D, the leading source of prescription drug coverage for dual Medicare and Medicaid beneficiaries.

Objectives: The study aimed to evaluate Medicare Part D's impact on use of fentanyl patches and use of less costly or less effective opioid medications among dual–eligible NH residents with cancer.

Methods: This quasi-experimental study included 4266 dual-eligible cancer patients admitted to 749 US NHs. We used nationwide data on NH resident health from the Minimum Data Set 2.0 linked to all-payer long-term care pharmacy dispensing records (January 2005 to June 2007) to estimate changes in the receipt of fentanyl patches, other strong opioids, and weak opioids after the January 2006 implementation of Medicare Part D. For each medication category, we calculated monthly proportions of NH residents receiving ≥1 prescription. Segmented Poisson regression estimated immediate and trend changes in medication use after Medicare Part D, adjusting for baseline trends.

Results: We observed increasing trends for all opioid medication categories prior to Medicare Part D. After Medicare Part D, receipt of fentanyl patches and other strong opioids abruptly decreased by 12% and 10%, respectively. Trend analyses indicate that dual-eligible NH residents were less likely to receive fentanyl patches after Medicare Part D relative to historical trends (incidence rate ratio [IRR], 0.99; $p=0.005$) but more likely to receive other strong opioids (IRR, 1.01; $p=0.02$) and weak opioids (IRR, 1.01; $p=0.004$).

Conclusions: We observed immediate and sustained reductions in the receipt of fentanyl patches and other opioids in dual-eligible NH residents with cancer after Medicare Part D implementation. Although the clinical impact of these patterns is uncertain, these findings suggest cost–related barriers to therapeutic options in the treatment of cancer pain in NHs.

232. The potential impact of the leucovorin shortage on U.S. Medicaid utilization and spending from 2008 to 2013

Ying Xia,[1] Boyang Bian,[2] Christina ML Kelton,[3] Jeff J Guo.[1] *[1]James L. Winkle College of Pharmacy, University of Cincinnati, Cincinnati, OH, USA [2]Health Economics, Humana Inc., Louisville, KY, USA [3]Carl H. Lindner College of Business, University of Cincinnati, Cincinnati, OH, USA*

Background: Both leucovorin (LV) and levoleucovarin (LLV) are folic acid analogs used to mitigate the side effects of methotrexate and other chemotherapy agents. Since April 2010, a majority of oncologists reported being unable to prescribe LV consistently due to shortages. LLV was approved by the FDA in March 2008 and is an alternative to LV in many cancer treatments.

Objectives: The purpose of this study was to determine any potential impact of the LV shortage on Medicaid utilization and spending on LV and LLV.

Methods: A retrospective, descriptive study was conducted using the national Medicaid pharmacy file for outpatient drug utilization maintained by the Centers for Medicare and Medicaid Services. Quarterly prescription counts, and (pre-rebate) reimbursement data from 2008 to 2013 were extracted for both LV and LLV. Average reimbursement per prescription was calculated by dividing reimbursement by the number of prescriptions.

Results: The total number of LV prescriptions rose from 34 915 in 2008 to 58 417 in 2013, representing a 67.3% increase, higher than the 23.4% increase in

the number of Medicaid beneficiaries (from 44.9 million to 55.4 million) over the same time period. Meanwhile, the total number of LLV prescriptions increased from 301 in 2009 to 13 116 in 2013, representing a 42.6-fold increase. In 2013, Medicaid spent $13.9 million and $6.7 million on LLV and LV, respectively. In 2013 quarter 4, the average reimbursement per prescription was $1116 for LLV versus $119 for LV.

Conclusions: Despite the national shortage, the number of LV prescriptions in Medicaid increased substantially over the last 6 years. If we were to ascribe all of the LLV prescriptions to the LV shortage, the cost to Medicaid of the shortage was approximately $13.1 million in 2013. However, the increasing utilization of LLV could also be explained by other factors such as better effectiveness and physician preference.

233. Utilization and spending trends for diuretics in the U.S. Medicaid program: 1991–2011

Amarsinh M Desai,[1] Jeff J Guo,[1] Christina ML Kelton,[2] Pamela C Heaton,[1] Teresa M Cavanaugh.[1] *[1]College of Pharmacy, University of Cincinnati, Cincinnati, OH, USA [2]College of Business, University of Cincinnati, Cincinnati, OH, USA*

Background: Diuretics have been effectively used to treat patients with cardiovascular disease. They are first-line agents for patients with hypertension or heart failure.

Objectives: This study aims to analyze the utilization and spending trends for diuretics in the U.S. Medicaid program over the past two decades.

Methods: A retrospective, descriptive time-series analysis was performed using the publicly available national Medicaid pharmacy files maintained by the Centers for Medicare and Medicaid Services. The study period was from 1991 quarter 1 through 2011 quarter 2. Utilization and expenditure data were obtained for the various classes of diuretics including thiazide and related diuretics, loop diuretics, potassium-sparing diuretics, carbonic anhydrase inhibitors (CAIs), and osmotic agents.

Results: The total number of prescriptions for diuretics doubled from 8.8 million in 1991 to 17.8 million in 2005, driven by a rise both in the number of Medicaid beneficiaries and in the prevalence of cardiovascular disease. However, by 2011, the number dropped substantially because of the movement of beneficiaries dually eligible for Medicare and Medicaid to Medicare starting in 2006 with the implementation of Medicare Part D. From 1991 to 2011, the prescription market share of thiazide and related diuretics increased from 21.6% to 51.0%. There was a decline in market share for potassium-sparing agents, loop diuretics, and CAIs from 14.5%, 61.2%, and 2.7% to 8.9%, 38.9%, and 1.0%, respectively. Medicaid spending on diuretics increased from $70.7 million to $144.2 million from 1991 to 2005 and then fell substantially. For thiazide and related diuretics, spending per prescription decreased from $8.66 in 1991 to $5.75 by the end of the study period.

Conclusions: Although growth in public spending on diuretics was substantial over the last two decades, the primary burden has shifted from Medicaid to Medicare. Over half of the prescriptions being reimbursed for Medicaid beneficiaries were for thiazide and related diuretics in 2011.

234. Type 2 diabetes treatment patterns across Europe

Edith M Heintjes,[1] Jetty A Overbeek,[1] Patrick Blin,[2] Gillian C Hall,[3] Francesco Lapi,[4] Daniel Prieto Alhambra,[5] Irene D Bezemer.[1] *[1]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands [2]Département de Pharmacologie, University Bordeaux Segalen, Bordeaux, France [3]Grimsdyke House, Barnet, UK [4]Health Search, Genomedics SRL, Firenze, Italy [5]Idiap Jordi Gol Primary Care Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain*

Background: Electronic healthcare databases can be used as source to assess drug treatment patterns followed by T2DM patients in real-life conditions.

Objectives: The objectives of the study were to describe the sequential treatment classes of type 2 diabetes (T2DM) patients initiating antidiabetic drug therapy in the Netherlands, United Kingdom (UK), Spain, Italy and France and to describe treatment scaling (intensification or de-intensification) in the overall T2DM population.

Methods: Antidiabetic drug use during a 5-year study period (2007–2011/2008–2012) ($n = 639{,}088$) was

obtained from electronic healthcare databases. A standardized analytic tool performed treatment pattern analyses in each database for the overall population and those initiating treatment. Oral monotherapy was defined as first line, oral dual therapy as second line, multiple oral treatments or oral in combination with an injectable as third line and injectables only as fourth-line therapy.

Results: Newly treated patients represented 33–42% of the overall T2DM population. Metformin monotherapy was the most common initial therapy (65–87%). Around 35% (the Netherlands, Italy and the UK) to 45% (Spain and France) switched treatment within the study period. The first switch was most often to metformin plus a sulfonylurea (SU) in the Netherlands (47%), the UK (45%), Spain (22%) and Italy (17%) but to DPP4 inhibitors in France (15%). DPP4 inhibitor use increased during the study period (France 0–27%, the UK and Spain <1– 9%) but remained limited in the Netherlands (4%) and Italy (2%).

In the total cohort, first-line treatment was most prevalent over all the years in all countries (around 50%). Intensification was the most common switch. Switching patients mostly stepped up or down one line at a time, but larger steps were also observed. Fourth line therapy was uncommon in France (1–2%) but accounted for about 10% in the other countries.

Conclusions: SU remained the most common add-on treatment to metformin in most European countries, while DPP4 inhibitor use was common in France and increased in other countries. Most T2DM patients are treated with oral monotherapy.

235. Estimating the impact of a breast cancer diagnosis on antidepressant adherence

Yi-Ting Chou,[1] Aaron N Winn,[2] Donald L Rosenstein,[3] Stacie B Dusetzina.[1] *[1]Division of Pharmaceutical Outcomes and Policy, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [2]Department of Health Policy Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [3]Departments of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Background: Depression is associated with lower quality of life and increased morbidity and mortality. Chronic treatment with antidepressants can lessen the symptoms of depression, but health-related crises – such as a cancer diagnosis – may disrupt ongoing depression care.

Objectives: The study aimed to estimate the effect of receiving a breast cancer diagnosis on antidepressant adherence among women with depression.

Methods: We used SEER-Medicare claims and included women aged 65 years and older with newly diagnosed breast cancer during 2008–2009, who were diagnosed with depression and used antidepressants for at least the year before the cancer diagnosis. To estimate the association between a breast cancer diagnosis and antidepressant adherence, we compared adherence among women with breast cancer and age-, month-, and year-matched controls without cancer. The outcome of interest was antidepressant adherence, as estimated by the proportion of days covered (PDC) before and after the index date. We considered patients to be adherent if PDC was over 80%. We compared adherence among patients with and without a cancer diagnosis using a difference-in-differences model.

Results: There were 784 women diagnosed with both breast cancer and depression, and 784 matched controls included. Patient characteristics were similar between the two groups, including median PDC (0.73 vs 0.74, $p=0.07$) in the 1-year pre-diagnosis period. A breast cancer diagnosis was associated with a 3.6% increase in the PDC after adjusting for patient characteristics (aRR: 1.04, 95%CI [1.02, 1.05]). Although PDC increased following breast cancer diagnosis, less than half of the patients were adherent.

Conclusions: Patients newly diagnosed with breast cancer had higher antidepressant adherence for pre-existing depression than those without breast cancer. Prior research has suggested that cancer diagnoses may disrupt adherence for other chronic conditions. Our findings were contrary to this prediction, which may be due to closer management of depression among newly diagnosed breast cancer patients or increased use of antidepressants for off-label or non-depression indications such as neuropathic pain or hot flashes among women with breast cancer.

236. Trends in the utilization of warfarin and the new oral anticoagulants in atrial fibrillation patients

Abdullah Abdulaziz Alalwan,[1] Stacy A Voils,[2] Abraham Hartzema.[1] *[1]Pharmaceutical Outcomes and*

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Policy, University of Florida, Gainesville, FL, USA [2]*Pharmacotherapy and Translational Research, University of Florida, Gainesville, FL, USA*

Background: Warfarin has been used for more than 60 years as an anticoagulant to decrease the risk of stroke and death among atrial fibrillation patients. In recent years, the FDA has approved three oral anticoagulants that may resolve challenges associated with warfarin administration.

Objectives: The aim was to determine the utilization of oral anticoagulants (OACs) among AF patients treated with warfarin, dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis).

Methods: A cross-sectional and longitudinal analysis was undertaken using Truven Health Analytics data for Medicare claims data. The study included beneficiaries aged 65 years and older who used OACs for atrial fibrillation or atrial flutter. The overall utilization of oral anticoagulation treatment in atrial fibrillation patients and the annual prevalence in OACs use (warfarin and the new OACs) were estimated based on pharmacy claims from 2008 to 2012.

Results: We identified 525 673 patients with atrial fibrillation between 2008 and 2012. The prevalence of warfarin use decreased from 599.43 in 2008 to 407.07 in 2012 per 1000 patients. The prevalence of dabigatran use increased six folds from 11.51 in 2010, the year of its approval, to 60.19 in 2012. The prevalence of rivaroxaban increased about 25 folds since its introduction to the market in 2011–2012.

Conclusions: The prevalence of warfarin declined between 2008 and 2012 in a Medicare population. The prevalence of the new OACs showed a significant growth in the uptake of dabigatran and rivaroxaban. There is limited data on apixaban in our database due to its more recent approval.

237. Utilization and predictors of psychotropic polypharmacy in adult patients with attention-deficit/hyperactivity disorder

Wei Liu, Xinyue Liu, Paul Kubilis, Yan Li, Yanmin Zhu, Almut G Winterstein. *Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA*

Background: Data on treatment with psychotropic polypharmacy in adult ADD/ADHD patients are sparse in the literature.

Objectives: This study examined polypharmacy rates and patterns in 29-state Medicaid data over a 12-year period (1999–2010).

Methods: Each year, adult beneficiaries were included if they were 18–64 years old, continuously eligible for the entire 12 months of the study year, and had ≥2 inpatient or outpatient ICD9-CM codes 314.xx. The following drug classes were analyzed: ADHD medication (stimulants or atomoxetine), antidepressants, antipsychotics, anticonvulsants, anxiolytics/hypnotics/sedatives, and lithium. Polypharmacy was assumed if patients received drugs from ≥2 drug classes concomitantly for ≥40 days. We report the top five medication class combinations used in each year. Multiple logistic regression with adjustment for age, sex, race, state, year, and mental health diagnoses was performed to identify predictors of polypharmacy.

Results: Eligible subjects increased dramatically from 3181 in 1999 to 60 467 in 2010 (mean age 26 years), a growing trend partially due to inclusion of Medicaid encounter data after 2007. Overall, prevalence of psychotropic polypharmacy use increased from 24% in 1999 to 37% in 2010. The most frequently dispensed combinations included ADHD drugs with antidepressants, ADHD drugs with antipsychotics, and ADHD drugs with anticonvulsants. Compared with patients who used monotherapy, subjects who took polypharmacy were more likely to be older age, male, and Caucasians, and they were less likely to have a history of severe mental illness including schizophrenia, bipolar disorder, and substance abuse.

Conclusions: Among adult ADHD patients enrolled in state Medicaid program, the proportion of subjects who were treated with psychotropic polypharmacy increased steadily from 1999 to 2010. Because the general effectiveness and safety of these combinations have not been formally tested, future studies should focus on comparative effectiveness and safety of those common combinations.

238. Withdrawn by author

239. Withdrawn by author

240. Dispensing of non-tamper-deterrent brands of oxycodone close to the Canadian USA border

Tara Gomes,[1] David Henry,[2] Mariam Mukati,[3] Michael Paterson.[4] [1]*St Michael's Hospital and the*

Institute for Clinical Evaluative Sciences, Toronto, ON, Canada [2]University of Toronto and the Institute for Clinical Evaluative Sciences, Toronto, ON, Canada [3]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada [4]Institute for Clinical Evaluative Sciences and McMaster University, Hamilton, ON, Canada

Background: Since 2010, tamper-deterrent long-acting oxycodone has been available in both the USA and Canada. However generic, non-tamper-deterrent brands of oxycodone were only introduced in Canada.

Objectives: We aimed to determine if the availability of non-tamper-deterrent oxycodone in Canada led to increased sales from Canadian pharmacies close to the USA border, which might be indicative of cross-border trafficking.

Methods: Using the IMS Brogan Geographic Prescription Monitor database, we conducted an analysis of long-acting oxycodone dispensing trends in Canadian community pharmacies in geographic areas contiguous with 113 Canada–USA border crossings between 1st February 2012 and 31st January 2014.

Results: Over the study period, 8 507 882 long-acting oxycodone tablets were dispensed by Canadian pharmacies in regions close to the US border. Following the introduction of generic long-acting oxycodone, the rate of long-acting oxycodone dispensing reduced in the border regions of the most populous provinces, Ontario British Columbia and Quebec, and rose slightly in Manitoba (4.4%) and New Brunswick (3.6%). Long-acting oxycodone dispensing rates rose by 45.5% in the border regions of Alberta and 92.3% in Saskatchewan; however, only 3341 long-acting oxycodone tablets dispensed were for the generic non-tamper-deterrent formulations. Examination of the dispensing patterns in 50 border areas after the marketing of non-tamper-deterrent oxycodone brands in Canada revealed no patterns suggestive of trafficking.

Conclusions: There were no large increases in the dispensing rates of prescriptions for generic non-tamper-deterrent long-acting oxycodone in Canadian pharmacies close to 113 Canada–US border crossings such as were seen at the Detroit Windsor Tunnel after the withdrawal of OxyContin in the USA in 2010.

241. Prevalence of switching from brand to generic asthma medications in the Netherlands

Marjolein Engelkes,[1] Nico C van Blijderveen,[1] Katia MC Verhamme,[1] Jetty A Overbeek,[2] Josine G Kuiper,[2] Ron CM Herings,[2] Miriam CJM Sturkenboom,[1] Johan C de Jongste,[3] Hettie M Janssens.[3] *[1]Medical Informatics, ErasmusMC, Rotterdam, The Netherlands [2]PHARMO Institute for Drug Outcomes, Utrecht, The Netherlands [3]Pediatrics Division of Respiratory Medicine and Allergology, ErasmusMC Sophia Childrens Hospital, Rotterdam, The Netherlands*

Background: The expiration of patents for brand asthma medications and ongoing pressure on the healthcare budget resulted in a growing market for generic medications. Switching of inhaled drugs implicates change of inhalation device. Few data are available on the prevalence of switching from brand to generic asthma drugs.

Objectives: The study aimed to investigate the use of brand and generic respiratory drugs and to describe the prevalence of switching between brand and generic respiratory drugs in patients with asthma in the Netherlands.

Methods: From the Dutch PHARMO Database Network, all dispensing of respiratory drugs with generic availability between 2003 and 2012 of asthma patients aged >5 years (without COPD diagnoses) was extracted. The prevalence of dispensing was calculated as percentage of users per calendar year per asthma drug and all asthma drugs combined. Switching was defined as mixed dispensing: generic after brand dispensing or vice versa.

Results: The cohort included 31 295 paediatric and 54 324 adult users with in total 380 510 dispenses over 2003–2012. All drugs combined, the percentage of children only using brand drugs decreased from 73% in 2003 to 54% in 2012, while only generic use increased from 8% to 17% and mixed use (both brand + generic dispenses) from 19% to 29%. Results for adults were similar; the percentage of adults with only brand dispenses decreased from 77% in 2003 to 72% in 2012, with only generic drugs increased from 7% to 9% and with mixed dispensing from 16% to 19%. In 2012, the proportion of generic dispensing was highest for Salbutamol, 53% in children and 51% in adults.

Conclusions: Dispensing of generic respiratory drugs in patients with asthma was significantly increasing. This might be due to introduced preferential policy of the Dutch healthcare insurances. Critics fear that non-consented switching to generic drugs may end up costing more in other aspects of asthma care, because the change of inhalation device may increase confusion and mistakes in inhalation technique, causing less effective treatment and lower adherence. Further research of switching is needed to investigate its potential consequences.

242. Withdrawn by author

243. Using group-based trajectory models to characterize longitudinal patterns of spending phenotypes and predict high-cost patients using medication use and comorbidity characteristics

Julie C Lauffenburger,[1] Jessica M Franklin,[1] Alexis A Krumme,[1] William H Shrank,[2] Olga S Matlin,[2] Claire M Spettell,[3] Gregory Brill,[1] Niteesh K Choudhry.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [2]CVS Caremark, Woonsocket, RI, USA [3]Aetna, Hartford, CT, USA*

Background: Predicting healthcare costs is important to identify patients for early intervention. Current approaches have poor discriminative ability and reduce potentially dynamic spending patterns into single values.

Objectives: The aims were to evaluate group-based trajectory models used to classify patients by their long-term spending phenotypes and predict high-cost patients and trajectories using patterns of medication use and comorbidity characteristics.

Methods: We used claims from a large national insurer and included a 50% random sample of all patients who filled at ≥1 pharmacy and medical claim between 2009 and 2011 and who had continuous eligibility for 2 consecutive years. Demographic, clinical, and medication use characteristics were measured in the baseline year. Costs were measured monthly in year 2 and were logarithmically transformed. We compared the discriminative ability of models that categorized patients with spending greater than or equal to the top fifth percentile as "high cost" with a novel approach using trajectory modeling of 2–7 groups. Ten-fold cross-validated *c*-statistics were used to compare the addition of baseline characteristics.

Results: Of the 498 871 patients, the top fifth percentile had costs exceeding $25 000/year. The seven-group trajectory model fit the data best, identifying a "high-cost" spending phenotype consisting of 31.4% of the patients. The *c*-statistic for the model predicting the top fifth percentile of yearly mean costs including all baseline predictors was 0.803 versus 0.821 for the "high-cost" spending trajectory model phenotype. In addition, adding in pharmacy characteristics explained 1.9% and 5.1% of the model variation for the top fifth percentile and high-cost trajectory models, respectively.

Conclusions: While high-cost patients defined using standard approaches were identified well by baseline characteristics, including medication use predictors, the performance of trajectory models was superior. Group-based trajectory models may be useful for identifying high-cost patients for cost containment and intervention.

244. Diagnosis and management of premenstrual syndrome in UK general practice: a study using the health improvement network

Cormac J Sammon, Irwin Nazareth, Irene Petersen. *Department of Primary Care and Population Health, University College London, London, UK*

Background: Premenstrual syndrome (PMS) is a prevalent condition; community estimates suggest 50–90% of women suffer some premenstrual symptoms, 10–30% suffer symptoms which impact on daily life and as much as 20% suffer severe symptoms. A range of pharmacological treatments have been suggested for the treatment of PMS. Despite this, there is little information on the prevalence and pharmacological management of the syndrome in primary care settings.

Objectives: The aim of the study was to investigate the rate of recording of PMS diagnoses in UK primary care and pharmacological treatments initiated following diagnosis.

Methods: Using The Health Improvement Network (THIN), all women with PMS diagnostic codes recorded were identified, and the incidence rate of first PMS records per 1000 person years (PY) was calculated, stratified by calendar year and age. Among women with a first PMS record, the proportion with a potentially PMS-related prescription (selective serotonin reuptake inhibitors, progestogen, oestrogen, oral contraceptive, gonadotrophin-releasing hormone agonists, danazol and vitamin B6) in the 6 months before the PMS record was identified, and among non-prevalent users, the proportion with a prescription on the day of diagnosis and in the 24 months after was identified.

Results: The rate of PMS diagnoses decreased over calendar time from 7.9 per 1000 PY in 1995 to 1.3 in 2013. Of women with a diagnosis, 10% received a potentially PMS-related prescription in the 6 months before the diagnosis. Of the 36 117 women without treatment in the 6 months prior, 56% received a potentially PMS-related prescription on the day of diagnosis (20% SSRI, 15% progestogen, 11% oestrogen and 15% other), and 82% received a potentially PMS-related prescription in the 24 months after diagnosis (41% SSRI, 30% progestogen, 20% oestrogen and 30% other). Between 1995 and 1999, the majority of women initiated a progestogen/oestrogen after a PMS diagnosis; after 1999, the majority initiated SSRIs.

Conclusions: There was a significant decrease in the rate of recording of PMS diagnoses over time. Many of the women with a diagnosis of PMS received pharmacological treatment, with SSRIs being the most common.

245. Therapeutic class differences in generic usage

Jodi B Segal,[1] Matthew Daubresse,[1] Chia-Ying Lee,[1] Mischka Moechtar,[1] Sarah Duchter,[3] Wenlei Jiang,[3] Robert Romanelli.[2] *[1]Johns Hopkins University, Baltimore, MD, USA [2]Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA [3]Office of Generic Drugs, U.S. Food and Drug Administration, Silver Spring, MD, USA*

Background: Despite the widespread availability of generic drugs and favorable costs, their uptake by prescribers and consumers remains incomplete.

Objectives: The study aimed to quantify the generic utilization rates (GURs) and generic substitution rates (GSRs) across high-priority therapeutic classes.

Methods: Using MarketScan Commercial Claims and Encounters, we characterized generic drug use among commercially insured Americans from 2010 to 2012. We prioritized classes including drugs having narrow therapeutic indices, high utilization, suspected generic underuse, and high rates of coupon use. For each class, we calculated the GSR and the GUR as the proportion of days with generic coverage within select 7-day windows. The GSR is the days covered by a generic divided by the total days covered by a generic or brand when generic is available. The GUR is the days covered by a generic divided by the total days covered by a generic or brand regardless of generic availability.

Results: We analyzed 27 classes with roughly 38-million days of drug coverage per 7-day window. In August 2010, the weighted average of the GURs across classes was 54%, while the weighted average of the GSRs was 64%. By November 2012, the GURs averaged 70%, and the GSRs averaged 81%. In both early and late windows, the GURs and GSRs diverged markedly in two classes: Adrenal hormones had a GUR of 2.7% and a GSR of 87%; these rose later to 10% and 97%. Similarly, androgens had an early GUR of 18% and a GSR of 86% that later were 24% and 81%. Across other classes, the GUR was modestly less than the GSR except when both neared 100%, as was so for antiemetics and antimanics. Other classes with low GURs and GSRs in 2010 were antiplatelets and sympathomimetics, with rates under 10%. By 2012, antiplatelets had a GUR of 83% and a GSR of 97%.

Conclusions: Generic drug usage differs by class. The class GSR exceeds the class GUR when there are many branded products without generics or many generics appropriate for therapeutic substitution. For small classes with few options for therapeutic substitution (like thyroid hormones), the GSR and GUR are more equivalent. The sympathomimetic class finding may be due to the restriction of generic albuterol with chlorofluorocarbons in their propellants.

246. Analgesic use in a Norwegian general population: change over time and high-risk use. A repeated cross-sectional study: the Tromsø Study

Per-Jostein Samuelsen,[1,2] Lars Slørdal,[3,4] Ulla Dorte Mathisen,[5] Anne Elise Eggen.[2] *[1]Regional Medicines*

Information and Pharmacovigilance Center (RELIS), University Hospital of North Norway, Tromsø, Norway [2]Department of Community Medicine, UiT – The Arctic University of Norway, Tromsø, Norway [3]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway [4]Department of Clinical Pharmacology, St. Olav University Hospital, Trondheim, Norway [5]Section of Nephrology, University Hospital of North Norway, Tromsø, Norway

Background: Increased use of analgesics in the population is a cause for concern in terms of drug safety. Although much is known about the risks associated with analgesic use, we are lacking knowledge on high-risk use at a population level.

Objectives: The objective of this study was to estimate the prevalence of analgesic use, including non-prescription (OTC) and prescription (Rx) drugs, change over time and the prevalence in the presence of potential contraindications and drug interactions in a general population.

Methods: A repeated cross-sectional study with data from participants (30–89 years old) of the Tromsø Study in 2001–2002 (Tromsø 5; $N = 8039$) and in 2007–2008 (Tromsø 6; $N = 12\,981$). Participants reported use of OTC and Rx analgesics and regular use of all drugs in the preceding 4 weeks. Change in use over the time period was analyzed with generalized estimating equations. The prevalence of regular analgesic use in persons with or without a clinically significant contraindication or drug interaction was determined in the Tromsø 6 population, and differences were tested with logistic regression.

Results: Analgesic use increased from 54% to 60% in women (OR = 1.24, 95%CI [1.15, 1.32]) and from 29% to 37% in men (OR = 1.39, 95%CI [1.27, 1.52]) in the time period; the increase was due to sporadic use of OTC analgesics. There was substantial regular use of analgesics in several of the contraindication categories examined; the prevalence of non-steroidal anti-inflammatory drugs was more than 8% among persons with chronic kidney disease, gastrointestinal ulcers or high primary cardiovascular risk. About 4% of the general population demonstrated at least one potential drug interaction with an analgesic drug.

Conclusions: The use of analgesics increased in the time period due to an increase in the use of OTC analgesics. Analgesic exposure in the presence of contraindications or drug interactions may put patients at risk. Public and prescriber awareness about clinically relevant contraindications and drug interactions with analgesics needs to be increased.

247. HIV treatment strategies in Europe (EU): adoption of single tablet regimen (STR)

Siva Narayanan,[1] Camelia M Graham,[2] Sarah Brown,[3] Samantha Fernando.[3] *[1]Evidence Generation, Value and Access Center of Excellence, Ipsos Healthcare, Washington, DC, USA [2]Evidence Generation, Value and Access Center of Excellence, Ipsos Healthcare, Boston, MA, USA [3]Ipsos Healthcare, London, UK*

Background: Once-daily STRs have become an increasingly popular choice for both newly initiating and treatment-experienced patients to improve patient adherence and achieve optimal outcomes.

Objectives: This study examines how STR prescribing trends have evolved in France, Germany, Italy, Spain, and the UK (big-5 EU), and provides insight into physician motivation to switch from conventional multi-pill antiretroviral (ARV) regimen dosing to STRs.

Methods: Multi-wave retrospective medical chart reviews of HIV patients have been conducted in the big-5 EU since 2005 to better understand patients initiating or switching ARVs during each quarter (Q) of the year. Physicians recruited from a large panel abstracted patient demographic, disease, and treatment data for consecutive HIV patients they encountered within a defined time period. This analysis focuses on STR prescribing trends from 1Q2009 to 1Q2014.

Results: Over 200 physicians abstracted an average of 3051 patient charts per quarter from 1Q2009 to 1Q2014. STR prescribing trends increased steadily in the big-5 EU from 17% in 1Q2009 to 23% in both 1Q2010 and 1Q2011 to 24% in 1Q2012 to 30% in 1Q2013 to 44% in 1Q2014. The top reason for switching from conventional ARV dosing to an STR across the big-5 EU in 1Q2009 was simplification (74%), followed by tolerability (14%), and patient decision (12%). Importance of tolerability in the decision to switch noticeably increased to 39% by Q12014, while in that same quarter, simplification had decreased to 49% and patient decision increased only slightly to 16%.

Conclusions: STR adoption in the big-5 EU increased rapidly, with simplification and an increased focus on tolerability emerging as the two most important reasons for switching from conventional ARV dosing from 1Q2009 to 1Q2014. These observed trends may emphasize the importance HIV providers have given towards maintaining HIV patients on a simple and yet tolerable regimen to achieve optimal adherence and clinical outcomes over the longer term.

248. Polypharmacy among older individuals with diabetes in Quebec, Canada

Caroline Sirois,[1,2] Marie-Eve Gagnon,[1] Céline Plante,[3] Marc Simard,[3] Isabelle Larocque.[3] *[1]Université du Québec à Rimouski, Lévis, QC, Canada [2]Centre d'Excellence sur le Vieillissement de Québec, Québec, QC, Canada [3]Institut National de Santé Publique du Quebec, Québec, QC, Canada*

Background: A significant proportion of older individuals suffer from diabetes. Treating diabetes and other comorbidites involves many medications, but there is little information on the actual pharmacological burden of the elderly population with diabetes.

Objectives: The study aimed to calculate the number of medications that older individuals with diabetes in Quebec, Canada, use annually and To identify the factors associated with polypharmacy.

Methods: We used Quebec Integrated Chronic Disease Surveillance System to build a population-based cohort of individuals aged 66 years and over who satisfy the diabetes case definition. We included individuals who were alive and covered by the Public Prescription Drug Insurance Plan between 1 April 2012 and 31 March 2013. We calculated the number of medications used at least once during the period for each individual. Individuals using 10 or more medications were considered exposed to polypharmacy. We used descriptive statistics to describe our cohort and used logistic regression to identify the factors associated with polypharmacy.

Results: The cohort comprised 230 052 individuals (mean age of 75.5 years, 50.4% male). A small proportion of patients were exposed to either no medication (1.77%, 99%CI [1.70, 1.84]) or 1–4 medications (5.80% [5.67, 5.93]). The majority of individuals (60%) used between 5–9 (29.00% [28.68, 29.26]) and 10–14 medications annually (32.18% [31.87, 32.48]), but significant proportions of individuals used 15–19 medications (18.44% [18.21, 18.68]) or 20 and more medications (12.84 [12.65, 13.03]). Overall, 145 999 individuals (63%) used at least 10 different medications in 2012–2013. More women than men were exposed to polypharmacy (68.2% vs 58.6%; $p < 0.0001$). Increased age, higher material deprivation and higher social deprivation were associated with polypharmacy ($p < 0.0001$).

Conclusions: About two-thirds of older individuals with diabetes in Quebec are exposed to a polypharmacy of at least 10 medications. There is a need to explore the quality of those polypharmacies to ensure optimal treatment and to minimize side effects.

249. Withdrawn by Author

250. Trends in asthma-related pharmacy fills

Karen E Wells,[1] Haejin Kim,[2] Suzanne Havstad,[1] Kimberley J Woodcroft.[1] *[1]Public Health Sciences, Henry Ford Health System, Detroit, MI, USA [2]Division of Allergy and Clinical Immunology, Henry Ford Health System, Detroit, MI, USA*

Background: National Asthma Education and Prevention Program guidelines recommend inhaled corticosteroids (ICS) plus a long-acting beta-agonist (LABA) as step-up therapy for the management of persistent asthma when ICS alone offers inadequate control of asthma symptoms. The advent of ICS/LABA in a single inhaler may have influenced prescribing trends over time.

Objectives: The aim of the study was to investigate the trends in asthma-related pharmacy fills and asthma exacerbations pre- and post-availability of ICS/LABA in a single inhaler.

Methods: Detailed longitudinal data on healthcare and medication use from a large covered patient population were used to assess rates of ICS ± LABA, short-acting beta-agonist (SABA), oral corticosteroid (OC) pharmacy fills, and asthma-related exacerbations. Analyses were limited to patients aged 12–56 years with a diagnosis of asthma between 1 January 1999 and 31 December 2011.

Patients with a recorded diagnosis of chronic obstructive pulmonary disease were excluded from rate calculations. Time trend analysis was used to identify changes in these rates over time.

Results: The analysis comprised 441 867 individuals and 199 797 filled prescriptions for asthma medications from 1 January 1999 to 31 December 2011. The rate of LABA as add-on therapy to ICS in separate inhalers peaked at 117 fills per 100 000 individuals in December of 1999. Within 2.5 years of FDA approval, the fill rate for ICS/LABA in a single inhaler surpassed the monthly rate of ICS fills. Since then, the average fill rate of ICS/LABA more than doubled that of ICS monotherapy (307 vs. 145 fills per 100 000). Rates of SABA fills dropped significantly ($p < 0.0001$) during the same period. Time trend analysis did not show a statistically significant change in rates of OC fills and asthma-related hospitalizations during the observation period ($p = 0.0545$, 0.3633 respectively), while asthma-related emergency department visits significantly increased over time ($p = 0.0018$).

Conclusions: ICS/LABA in a single inhaler is the most commonly prescribed asthma controller therapy since 2003. The symptom relief that the addition of LABA provides may motivate regular use, thereby reducing the need for SABAs. There was no reduction in the rate of asthma exacerbations over time.

251. Utilization, price, and spending trends for fluoroquinolones in the US Medicaid program: 1991–2013

Xiaomeng Yue, Jeff J Guo, Ying Xia, Ziyad S Almalki, Patricia R Wigle. *Division of Pharmacy Practice and Administrative Sciences, University of Cincinnati, Cincinnati, OH, USA*

Background: Fluoroquinolones are broad-spectrum antibiotics commonly used in the treatment of respiratory tract infections, uncomplicated urinary tract infections, and gastrointestinal infections.

Objectives: This study described and analyzes trends in the utilization, spending, and average per-prescription cost of fluoroquinolones individually and overall, by the Medicaid programs from 1991 to 2013.

Methods: A retrospective, descriptive analysis was performed using the publicly available national Summary Files from the Medicaid State Drug Utilization Data maintained by the Centers for Medicare and Medicaid Service. Study drugs included ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin, as well as recently withdrawn drugs, grepafloxacin (1999), sparfloxacin (2001), trovafloxacin (2001), and gatifloxacin (2006). Annual prescription counts and reimbursement amounts were calculated for all fluoroquinolones reimbursed by Medicaid. Average per-prescription spending as a proxy for drug price was calculated (estimated) for all generic and brand drugs by dividing reimbursement by the number of prescription.

Results: The total number of fluoroquinolone prescriptions rose 340% from 1.66 million in 1991 to 5.65 million in 2005 and then decreased to 4.21 million in 2013. Total expenditures on fluoroquinolones increased from $81 million in 1991 to $395 million in 2004 and then decreased to $163 million in 2013. The average pre-prescription price for generic ciprofloxacin was $7.76 in 2013, whereas the price per-prescription of branded (Cipro) ciprofloxacin was $149.34. The sharp decrease in the utilization of Trovan can be explained by the withdrawal from the market in 2001 because of risk of liver failure.

Conclusions: Increased expenditures for fluoroquinolones paralleled with increased utilization. Generic drug utilization increased dramatically after brand-name patent expiration. Fluoroquinolone drug utilization might be also associated with its safety profile and related disease treatment guidelines.

252. Trends of systemic antibiotics (AB) consumption in the community in Russian Federation (RF)

Ivan Zaharenkov,[1] Polina Antoshkina,[1] Svetlana Rachina,[1] Julia Belkova.[1] [1]*Department of Clinical Pharmacology, Institute of Antimicrobial Chemotherapy, Smolensk State Medical Academy, Smolensk, Russian Federation*

Background: AB consumption (Cons) surveillance is essential to improve their usage in clinical practice and combat antibiotic resistance.

Objectives: The study aimed to analyze the level and structure of systemic AB Cons in outpatient settings in RF over time.

Methods: Data containing products names, ATC/DDD codes and values, drug forms, dosages and number of packages were collected during pharmacy audit, 2001–2013. AB Cons (J01 group) was expressed as a number of defined daily doses/1000 inhabitants/day (DID).

Results: Outpatient AB Cons in 2001–2013 was as follows: 8.50, 9.8, 9.8, 9.4, 9.4, 9.6, 9.95, 10.2, 12.2, 12.2, 12.9, 12.9 and 12.6 DID. Proportion of penicillins (J01C), macrolides, lincosamides and streptogramins (J01F), quinolones (J01M) and other β-lactams (J01D) increased by 18.5, 7.4, 4.9 and 4.2%, respectively, while sulfonamides (J01E), tetracyclines (J01A) and aminoglicosides (J01G) decreased by 17.5, 10.6 and 3.2%. J01C Cons was characterised by increasing amoxicillin (AMO) and amoxicillin/clavulanate (AMC) and decreasing ampicillin use (from 0.44, 0.032 and 0.67 DID in 2001 to 3.01, 1.4 and 0.23 DID in 2013, respectively). Other β-lactams weight rose mainly due to third generation cephalosporins (CS) from 0.02 to 0.48 DID. As for J01F, erythromycin Cons decreased (from 0.27 in 2001 to 0.06 DID in 2013), whereas azithromycin and clarithromycin Cons had opposite trend (from 0.1 and 0.035 in 2001 to 1.4 and 0.5 DID in 2013, respectively). The J01M Cons increase was mainly due to ciprofloxacin and 'newer' fluoroquinolones (mainly levofloxacin and moxifloxacin) use (from 0.54 and 0.004 in 2001 to 1.07 and 0.25 DID in 2013, respectively).

Conclusions: A significant increase of total outpatient AB Cons and change of Cons patterns were revealed in RF. In the dynamics, both positive (decrease of J01E, J01A and J01G Cons and increase of AMO, AMC, 'newer' macrolides and fluoroquinolones weight) and negative (increase of third generation parenteral CS Cons) trends were observed.

253. Use of antidepressives and the economic crisis in Portugal

Claudia Furtado. *INFARMED, Lisbon, Portugal*

Background: The economic and financial crisis started in the end of 2008 and since 2011 Portugal is under an EU/IMF bailout programme, which introduced wage cuts and increased unemployment rate. The financial and social crisis may have had a negative effect on mental health, increasing the use of antidepressives.

Objectives: With this study, we aim to analyse antidepressive use at a national level and determine if there were changes in consumption trend as a consequence of the economic crisis.

Methods: Monthly data were collected from 2000 to 2014. Data refer to antidepressives prescribed and dispensed in outpatient care in the National Health Service (NHS). IMS Health data were also used to validate and complete NHS data.

Main outcome measure was the defined daily dose (DDD) per 1000 inhabitants per day (DID), and adjustments were made for the length of each month.

A segmented regression analysis of an interrupted time series was used to establish if there was a deviation from the underlying trend on antidepressives use since the implementation of memorandum of understanding (MoU) in May 2011.

We pre-specified a lag time by excluding outcome values, to allow the political measures to have effect (Stata version 11).

Results: Antidepressive use has been increasing over the last 14 years exceeding 90 DID in 2014. The model did not show a statistical significant ($p > 0.05$) change in the level of consumption, expressed in DID, due to the bailout programme.

However, it is important to evidence that the onset of financial crisis is difficult to establish, and this may have an impact on the results. To attenuate this potential bias, different hypotheses were tested (e.g. economic crisis started when the unemployment rate rose above 10%), and none seemed to change significantly the results.

Conclusions: The implementation of the MoU does not seem to have had an effect on the level and trend of antidepressives use.

To this fact, some explanations can be identified: social network and family support may have attenuated the impact of the economic instability on mental health, or the lack of economic resources may have decreased visits to doctors.

254. Trends in use of erythropoiesis-stimulating agents and blood transfusions in US hemodialysis patients with cancer

Anne M Butler, Abhijit V Kshirsagar, Andrew F Olshan, Matthew E Nielsen, Stephanie B Wheeler, M Alan Brookhart. *University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Background: Erythropoiesis-stimulating agents (ESAs) and blood transfusion are used to treat anemia

in both end-stage renal disease (ESRD) and cancer. However, anemia treatment patterns have not been described among ESRD patients undergoing hemodialysis (HD) with concurrent cancer, especially in the recent era of ESA-related safety concerns.

Objectives: The study aimed to describe trends in anemia management (2000–2010) in the US HD population after the diagnosis of cancer.

Methods: Using data from the US Renal Data System, a national registry of dialysis patients in the Medicare ESRD program, we identified patients ≥18 years old receiving incenter HD between 2000 and 2010 with Medicare as their primary payer and parts A and B coverage. We restricted the cohort to patients who received their first cancer diagnosis ≥9 months after dialysis initiation (≥2 ICD-9-CM diagnosis codes within 2 months). We used multivariable generalized linear models to estimate quarterly trends and patterns in ESA use, epoetin alfa (EPO) dose, and transfusion use as well as resulting hemoglobin levels.

Results: We identified 39 012 eligible HD patients with cancer who met study entry criteria. Quarterly ESA use remained constant between 92% and 94% from 2000 to 2010. Mean quarterly EPO dose increased from 2000 to 2004 and then declined; mean quarterly hemoglobin levels followed a similar pattern. There was an increase in quarterly transfusion use (6.6–9.5%) and mean number of transfusion days per year (1.4–1.8). Anemia treatment patterns also varied by demographic and clinical subgroups, especially among patients receiving chemotherapy, who required higher ESA use, EPO dose, and frequency of transfusions.

Conclusions: Despite safety concerns about ESAs in both the ESRD and cancer populations, the proportion of HD patients with cancer who used ESAs between 2000 and 2010 remained extremely common and remarkably constant. EPO dose and hemoglobin levels both increased and then decreased. Transfusions increased in frequency. Future research examining the risk–benefit profile of different anemia management strategies in the dialysis population with cancer is needed.

255. Drug utilization in rheumatoid arthritis from a large Japanese hospital administrative database

Bruce Crawford,[1] Joseph Kim.[2,3] *[1]IMS Health, Real-world Evidence Solutions, Tokyo, Japan [2]IMS Health, Real-world Evidence Solutions, London, USA [3]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK*

Background: Pharmacoepidemiological studies of biologic therapies for rheumatoid arthritis (RA) in the Japanese patient population to date have been limited. This lack of studies has been, in part, due to limited data availability.

Objectives: We, therefore, performed this drug utilization study of biologics and disease modifying antirheumatic drug (DMARDs) in a large Japanese claims database to better understand the real-world utilization of RA therapies within a Japanese population and to evaluate the usefulness of a hospital claims database for pharmacoepidemiologic research.

Methods: Prescription data for patients with RA (ICD-10 M05 or M06) were captured from a hospital claims database that contains detailed electronic hospital medical records across 147 Diagnosis Procedure Combination (DPC) hospitals in Japan, which was used. Data were extracted from September 2013 to August 2014. Distribution of treatments by age and gender and time on therapy was examined.

Results: A total of 13 256 patients were found to have RA and taking an anti-rheumatic agent during the year of data. Seventy-five percent were women with an average age of 63 years (range: 18–90 years), and 89% received their treatment in an outpatient setting. The distribution of monthly subscriptions was centred around 6 months/year with a spike at 12 monthly prescriptions. Only 20% of patients were using a biologic, with 66% using a DMARD (61% were using methotrexate alone), while 14% were using combination therapy. The youngest patients were using Remicade (56.01 years old) and the oldest Rituxan (69.45 years old). Biologic use occurred inpatient 20% of the time (14% for combination therapy patients), while traditional DMARDs were administered in an outpatient setting 92% of the time.

Conclusions: These data confirm the usefulness of hospital administrative data in Japan for drug utilization research, which can be further enhanced through linkage to healthcare resources, costs and clinical outcomes.

256. New oral anticoagulants in clinical practice: trends in prescribing patterns and health spending

Claudia Furtado. *Infarmed, Lisbon, Portugal*

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Background: A deeper look on the use of anticoagulants takes a particular interest due to the introduction of new oral anticoagulants (NOA).

Due to pharmacovigilance concerns, there is a need to monitor the use of NOA in real-world practice. Due to high cost, it is also important to monitor health spending in National Health Service (NHS) and most particularly patients spending.

Objectives: This study aimed to analyze the adoption of NOA in clinical practice and by type of prescribing doctor: general practitioners, specialists practicing in public hospitals and specialists practicing in private hospitals.

We also intended to assess the influence of European level decisions (approval of new therapeutic indications) and national reimbursement decisions on prescribing patterns and health spending.

Methods: Utilization and expenditure data from 2000 to 2014 was obtained from NHS reimbursement database. Utilization data were converted into defined daily dose (DDD) per 1000 inhabitants per day (DID).

Main outcome measures were DID, NHS and patient expenditure.

Results: Anticoagulants increased from 2.37 DID in 2000 to 10.5 DID in 2013. Although warfarin remains the most used, there was a sharp increase in the consumption of NOA. This was more pronounced at the end of 2011 due to approval of new therapeutic indications despite the fact that these new indications had not yet been subject to national reimbursement evaluation.

Regarding the type of practice, specialists working in private care were early adopters of NOA. At the end of 2013, Dabigatran accounted for 45% of all anticoagulants prescribed in private care. Specialist working in public hospitals showed a more conservative pattern, and NOA did not exceeded 15% of all anticoagulants.

In 2013, NHS expenditure with the Dabigatran (12.9 M €) was about seven times higher than that with Warfarin. Patients also had their co-payments increased: 1 month of treatment with warfarin on average cost patients 0.75€, while with Dabigatran or Rivaroxaban, it costed around 20€.

Conclusions: With increasing prescription of NOA, it is important to monitor potential adverse effects, health outcomes but also adherence to therapy due to the high costs of these new drugs for patients.

257. Urban–rural differences in the uptake of new formulations of osteoporosis drugs

Racquel Jandoc,[1] Muhammad Mamdani,[1,2,3,4] Linda E Lévesque,[5] Suzanne M Cadarette.[1,2] *[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada [3]Applied Health Research Center, La Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada [4]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada [5]Department of Public Health Sciences, Queen's University, Kingston, ON, Canada*

Background: Rural physicians may be less aware of public drug formulary changes listing new formulations due to their isolated practice and less exposure to specialist referrals and pharmaceutical promotion. This may result in regional differences in dispensing. We sought to examine the relative uptake of new formulations of osteoporosis medications: alendronate + vitamin D3 (listed: 2007/01), monthly risedronate (listed: 2009/06), and risedronate delayed-release (listed: 2012/02), between urban and rural regions.

Objectives: The study aimed to examine urban–rural differences in dispensing of new formulations of osteoporosis drugs.

Methods: We used Ontario healthcare data to identify osteoporosis drug claims dispensed from 2001/01–2014/03 to community-dwelling seniors (aged 65 years or older). We plotted the monthly proportion of new formulations (proportion of new formulation claims of all claims with the same drug molecule) from their formulary listing date until 2014/03. Results were stratified by urban, nonmajor urban or rural region as defined by the Rurality Index of Ontario, a rurality score that considers population size and local access to healthcare services. Differences in proportions and trends of dispensing over time were compared between regions using regression analysis.

Results: We identified 16 367 752 eligible claims (77% urban, 18% nonmajor urban and 5% rural). Rural regions consistently had a slower uptake and lower proportion of overall claims dispensed. For instance, an average of 18% of alendronate + vitamin D3 claims was dispensed in rural regions compared with 31% in nonmajor urban and 44% in urban regions. Similar trends were identified for monthly risedronate (26%

rural, 32% nonmajor urban and 39% urban) and risedronate delayed-release (15% rural, 22% nonmajor urban and 22% urban).

Conclusions: We identified significantly slower uptake and lower proportions of new formulations of osteoporosis drugs dispensed in rural regions compared with urban regions. Further research examining whether urban–rural differences in prescribing translate into regional differences in clinical outcomes is warranted.

258. Attitudes in statins use in Greece

Paraskevi Papaioannidou, Achilleas Ntaralas. *Department of Pharmacology, Medical Faculty, Aristotle University of Thessaloniki, Thessaloniki, Greece*

Background: Statins are prescribed widely to avoid cardiovascular complications in high-risk patients. Under the current financial crisis in Greece, an effort has been made by the Greek health authorities to encourage generic prescribing, in order to lower medicinal cost.

Objectives: The purpose of this work was to study attitudes in statins use and to calculate the use of generics in statins sales in a sample from the medicines market of Thessaloniki, the second largest city in Greece.

Methods: A sample of statins registered sales was collected using the new electronic health records that been applied during the last years in Greece. The sample corresponded to a small amount of sales from the market of Thessaloniki during the years 2012 and 2013, including only community and no hospital sales. All brand names (reference and generics) of statins and their relative ratios in the sales were estimated, and the percentage of generics in the sale of each medicine was calculated. The amount of medicines was estimated in defined daily doses (DDDs) of the reference drug and its generics.

Results: Simvastatin and atorvastatin sales corresponded to 81% of total statins sales with almost equal share in the market (41% and 40%, respectively). The percentage of sales for other statins was 13% for rosuvastatin, 4.5% for pravastatin, 1.4% for fluvastatin and less than 0.02% for lovastatin. Generic use corresponded to 66% of total sales (56 795 DDDs out of 86 103 DDDs), being 99.7% for simvastatin (35 442 DDDs out of 35 555 DDDs), 54% for atorvastatin (18 274 DDDs out of 33 856 DDDs) and 78% for pravastatin (3066 DDDs out of 3 913 DDDs).

Conclusions: In spite of the generally low use of generics in Greece, the percentage of generics in statins sales was very high in the study sample.

259. Drug use among elderly in the year before colon cancer diagnosis versus matched cancer-free controls

Felice N van Erning,[1,2] Marjolein MJ Zanders,[1] Myrthe PP van Herk-Sukel,[3] Josine G Kuiper,[3] Valery EPP Lemmens.[1,2] *[1]Research, Netherlands Comprehensive Cancer Organisation (IKNL), Eindhoven, The Netherlands [2]Public Health, Erasmus MC University Medical Centre, Rotterdam, The Netherlands [3]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands*

Background: The use of multiple drugs for coexisting diseases can lead to adverse drug reactions and interactions. When deciding on anticancer drugs in colon cancer patients, it is important to know which drugs are commonly used.

Objectives: The aims were to provide an overview of drugs used by elderly in the year before colon cancer diagnosis and to compare this with a matched control group without cancer.

Methods: Data were obtained from the population-based Netherlands Cancer Registry (NCR) and linked to the PHARMO Database Network, which includes complete longitudinal data obtained from outpatient pharmacies.

All colon cancer patients aged ≥70 years diagnosed between 2000 and 2011 were included. Cancer patients were matched 1:1 with controls on gender, year of birth and postal code. Differences in the proportion of users between cases and controls of each drug on WHO ATC-3 level were calculated using Chi^2 tests. Drug use was defined in the year before colon cancer diagnosis or cohort entry date and during each quarter of that year.

Results: The total study population consisted of 2735 elderly colon cancer patients and 2735 matched cancer-free controls. Ninety percent of cases and 69% of controls used at least one drug during the total study period. The top three most frequently used drugs,

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based on the highest number of users among cases during the total year, were drugs for constipation (cases vs. controls 58% vs. 10%, $p < 0.0001$), antithrombotic agents (42% vs. 33%, $p < 0.0001$) and drugs for acid-related disorders (35% vs. 22%, $p < 0.0001$). For all three drugs, the number of users in each quarter was higher among cases than that among controls. Furthermore, among cases, the number of users increased during the last quarter of the year for drugs for constipation (10% in Q3 to 53% in Q4) and drugs for acid-related disorders (19% in Q3 to 27% in Q4).

Conclusions: Our study demonstrates higher drug use among elderly colon cancer patients during the total year before diagnosis as compared with that of a matched cancer-free control group, which increased even more during the last 3 months before colon cancer diagnosis. The effect of specific drugs on cancer treatment and outcome should be subject to further study.

260. Prevalence of low cost generic program use in a nationally representative cohort of privately insured adults

Joshua D Brown, Nathan J Pauly. *Institute for Pharmaceutical Outcomes and Policy, University of Kentucky, Lexington, KY, USA*

Background: Medication exposure misclassification is a major limitation of using administrative claims for pharmacoepidemiological research. Low-cost generic programs (LCGPs) are a sparsely studied source of misclassification.

Objectives: The study aimed to determine the user prevalence and demographics of LCGP use in a nationally representative sample and to determine the most common medications used.

Methods: This is a cross-sectional study using the 2007–2011 Medical Expenditure Panel Survey. Subjects were included if they had only private insurance, were 18–64 years of age, and participated in all rounds of the survey. LCGP users were classified if they filled at least one medication through a program. Medications were identified if they were available through an LCGP, paid completely out of pocket with specific dollar amounts, and matched certain quantities dispensed. LCGP users and non-users were compared by age, race, gender, region, income level, comorbidity burden, and the number of prescriptions filled. Logistic regression was used to determine which factors were significant predictors.

Results: A total of 19 037 individuals were included in the study – representing about 93 million privately insured adults. LCGP users made up 36.4% of the cohort, increasing from 22.1% in 2007 up to nearly 40% in later years. Over 10% of all prescription fills were obtained through LCGPs. Over 30% of fills for antigout, metronidazole, ACE inhibitors, levothyroxine, metformin, and diuretics were obtained through these programs. Compared with the reference group aged 18–34 years, subjects 35–54 years old (odds ratio (OR) 1.39, 95%CI [1.29, 1.50]) and 55–64 years old (OR 1.86 [1.70, 2.04]) were more likely to be users. Females were also more likely than males to be users (OR 1.42 [1.33, 1.51]). Each unique medication class used also increased the odds of being an LCGP user by 18% (OR 1.18 [1.17, 1.19]).

Conclusions: There is high prevalence of LCGP use in the privately insured population. Exposure misclassification via LCGPs could impact studies investigating the harms or benefits of medications and studies of adherence or quality measures.

261. Gaps in ethical policies for the conduct of drug utilization studies to assess the effectiveness of risk minimization interventions

Caroline Tremblay,[1] Alia Yousif,[2] Aurore Bergamasco,[2] Yola Moride.[1,2] [1]*Faculty of Pharmacy, Université de Montréal, Montréal, QC, Canada* [2]*Yolarx Consultants Inc., Montréal, QC, Canada*

Background: Risk minimization interventions (RMIs) may be implemented to optimize drug benefit–risk in the real-world setting. Hence, many studies to assess the effectiveness of the RMIs involve drug utilization studies (DUS) with the objectives of measuring off-label use, presence of contraindicated concomitant drugs or comorbidity and appropriate monitoring, amongst others. In countries where no claims databases are available, such DUS involve review of medical charts or pharmacy records. The ethical requirements pertaining to the conduct of DUS involving *ad hoc* data collection appear to be heterogeneous across countries and settings.

Objectives: The aim of the study was to explore the ethical requirements within ICH countries for the conduct of DUS in hospital and ambulatory care settings.

Methods: Three strategies were used: (i) a review of existing legislative sources in the countries of interest; (ii) a review of the literature on DUS and extraction of ethical requirement information of relevant sources; and (iii) a survey sent to ethics committees and/or key informants that included three case studies: (i) a DUS involving medical chart review; (ii) a paediatric DUS, involving medical chart review and contact with patients' legal guardians; and (iii) a DUS conducted through community pharmacy records.

Results: The literature review has confirmed the great disparity across ethics committees worldwide. The ethical policies at the level of institutions are heterogeneous, since there is a lack of clearly defined and harmonized legislation on the implementation of DUS.

Conclusions: The lack of harmonization in the legislative and ethical framework for DUS across different countries highlights the challenges in the implementation of DUS, especially those that involve multiple countries.

262. Prescriptions errors in a random sample of Egyptian community pharmacies of the city of Alexandria

Omnia AbdelRahman,[1] Aida Reda,[2] Nessrin Elnimr,[2] Adel Abou-Ali.[3] *[1]Faculty of Pharmacy, Alexandria University, Alexandria, Egypt [2]High Institute of Public Health, Alexandria University, Alexandria, Egypt [3]Sanofi Pasteur, Toronto, ON, Canada*

Background: Any step in the prescribing process can generate errors, commonly as faults in dose selection and poor handwriting. Community pharmacists should do their best to ensure an error-free dispensing process.

Objectives: The study aimed to measure the percentage of wrong prescriptions dispensed by a random sample of 200 pharmacists in the city of Alexandria, Egypt.

Methods: In a cross-sectional survey, a random sample of 220 pharmacists employed at community pharmacies of different geographical areas of the city of Alexandria, Egypt, were selected to participate in the study. The survey was designed to collect information on the three types of dispensed prescriptions: prescriptions dispensed with no errors, prescription dispensed with minor errors and prescription dispensed with major errors.

Results: Participants age ranged from 20 to 74 years with a mean age of 31 years and mean years of experience of 9.2 years. The majority of participants (63.5%) were in the age group of 20–30 years old; 57.5% of participants participated in continuing education programmes, and 18.5% participated in a postgraduate programme. Four-hundred dispensed prescriptions were examined during the study. The percentage of prescriptions dispensed with no errors was 98.5%, 1.3% for prescriptions dispensed with minor errors and 0.3% for prescription dispensed with major errors. Among prescriptions with errors, 7.7% and 4.3% included errors with the dispensed dose quantity and frequency, respectively. In 56.3% of the dispensed prescriptions, the dispensing pharmacist did not provide information on special administration instructions to patients. Further, in 17.6% of dispensed prescriptions, the pharmacist did not inform patients of the correct storage conditions needed, and in 16.7%, wrong storage conditions were provided.

Conclusions: Even though the percentage of prescriptions dispensed with errors was fairly low, the percentages of prescription with no administration instructions and no storage or wrong storage instructions provided were high. Pharmacists should pay a careful consideration to administration and storage instructions provided to patients to ensure a safe and more effective way of medication use.

263. Assessing the completeness of data included on a random sample of medical prescriptions dispensed at local pharmacies in the city of Alexandria, Egypt

Omnia AbdelRahman,[1] Aida Reda,[2] Nessrin Elnimr,[2] Adel Abou-Ali.[3] *[1]Faculty of Pharmacy, Alexandria University, Alexandria, Egypt [2]High Institute of Public Health, Alexandria University, Alexandria, Egypt [3]Sanofi Pasteur, Toronto, ON, Canada*

Background: The amount of information included on a medical prescription can directly affect the dispensing process and impact the safety and effectiveness of prescribed medications.

Objectives: The study aimed to assess the completeness of data included on a random sample of 400

medical prescriptions dispensed at community pharmacies in the city of Alexandria, Egypt.

Methods: In a cross-sectional survey, a random sample of 220 community pharmacists from different districts of the city of Alexandria, Egypt, were selected to participate in the study. Two-hundred pharmacists of the selected sample have completed the questionnaire. The questionnaire was designed to collect information on important items that should be included on a medical prescription such as patient age, weight, allergies, diagnosis and dosage information (dose quantity, frequency, dosage form and duration of treatment).

Results: Four-hundred dispensed prescriptions were examined during the study, two per each participating pharmacist. Only 14.5% of the examined prescriptions included information on the patient's age, 4.3% included the patient's weight, 0.3% included information on the patient's allergies and 30.8% included information on the patient'0s diagnosis. The majority of the prescriptions examined (88.3%) included complete information on dose quantities, and 94.3% included complete information on dose frequencies. Complete dosage form information was included on 85% of examined prescriptions, 93.3% included complete information on medications' strength and 29% included information on treatment duration.

Conclusions: Apart from dosage information, a high percentage of the dispensed prescriptions were missing important information on patient age, weight, allergy and diagnosis. Complete information on patient age, weight, allergy and diagnosis is warrant to ensure a safe and effective use of medications. Prescribers in the city of Alexandria should pay careful attention to include such information on their medical prescriptions.

264. Trends in the medical consumption of strong opioid analgesics in Taiwan during years 2007 to 2011

Li-Fen Kuo,[1] Wen-Ing Tsay.[2] *[1]Food and Drug Administration, Ministry of Health and Welfare, Taipei City, Taiwan [2]Food and Drug Administration, Ministry of Health and Welfare, Taipei City, Taiwan*

Background: Pain has been a worldwide and important medical concern. Narcotic drugs are mainly used for pain relief, and morphine consumption has been proposed by World Health Organization (WHO) as an important indicator of a country's progress in cancer pain relief.

Objectives: This study explored the medical consumption trends of three strong opioids (morphine, fentanyl and pethidine) in Taiwan during years 2007 to 2011.

Methods: The three most commonly prescribed strong opioid analgesics, morphine, fentanyl and pethidine, in Taiwan were analyzed in this study. The medical consumption of the investigated opioids 2007–2011 was extracted from the databases of the controlled drug management system of Taiwan's Food and Drug Administration. The data were converted into defined daily doses for statistical purposes per million inhabitants per day (S-DDD/m/d) using Taiwan Ministry of Interior Statistics population data. Further, the study made the multi-country comparisons with the official data (S-DDD/m/d) from the International Narcotics Control Board (INCB).

Results: During years 2007–2009, 2008–2010 and 2009–2011, the S-DDD/m/d of morphine in Taiwan was 153, 161 and 169, respectively. It was lower than the USA (2060/2045/2092), Canada (2080/1918/2061), the UK (1114/1449/1511) and Australia (1381/1355/1339) but higher than Japan (76/72/70). The S-DDD/m/d of fentanyl in Taiwan (421/508/537) was less than that in Germany (12 772/12 642/12 717), the USA (9904/9262/8380), Canada (9432/9718/11 288), France (5055/5477/5624) and Japan (805/935/1009). The S-DDD/m/d of pethidine fell in Taiwan (20/19/18), the USA (88/80/66), Australia (31/26/22) and Germany (14/11/10), and it was stable in France (1/1/1) and Japan (3/3/3).

Conclusions: In years 2007–2011, strong opioid consumption increased moderately in Taiwan. It was much lower than in major developed countries, suggesting that there is room for growth in the consumption of opioids in Taiwan. In addition, the fall in pethidine consumption in Taiwan is very minor (10%) and much smaller than the decline in other countries.

265. The burden of cardiovascular disease and the impact of anti-diabetic medication on incident cardiovascular disease in patients with type 2 diabetes: findings from U.S. National Surveys

Longjian Liu,[1] Hui Liu.[2] *[1]Epidemiology and Biostatistics, Drexel University School of Public Health,*

Philadelphia, PA, USA [2]Epidemiology and Biostatistics, Drexel University School of Public Health, Philadelphia, PA, USA

Background: Studies, using a large-scale population sample size, that examined associations between anti-diabetic and anti-dyslipidemia medications and risk of cardiovascular disease (CVD) in patients with type 2 diabetes (T2DM) were limited.

Objectives: We aimed to examine the associations and test potential differences by age, race and ethnicity.

Methods: We analyzed a national combined dataset from 2009 to 2011 Medical Expenditure Panel Surveys linked to National Health Interview Surveys in participants aged 30 years and older ($n = 35\,838$). T2DM, coronary heart disease (CHD), and stroke were identified by ICD-9 codes. Incident CVD (CHD and stroke) in T2DM patients were classified for those who had CVD diagnosed after T2DM.

Results: In T2DM patients, Blacks had significantly higher prevalent CHD and stroke after aged 55 years than Whites. The corresponding values for prevalent CHD were 6.0% vs. 3.9% ($p = 0.01$), 12.3% vs. 6.8% ($p < 0.0001$), 22.6% vs. 7.6% ($p = 0.01$) for Blacks vs. Whites aged 55–64, 65–74, and 75 years or above, respectively, and for prevalent stroke were 4.8% vs. 1.5% ($p < 0.0001$), 7.6% vs. 3.7% (<0.001), and 7.6% vs. 3.4%, respectively. Blacks had significantly higher incident CHD (7.0% vs. 4.7%, $p = 0.02$) and stroke (3.1% vs. 1.6%, $p = 0.01$) than Whites. T2DM patients with anti-diabetic therapy had significantly lower incident CHD than those without anti-diabetic therapy (odds ratio = 0.58 and 95%CI [0.37, 0.74], $p = 0.025$). In patients with T2DM, the top three frequent anti-diabetic medications were non-sulfonylureas, sulfonylureas, and insulin in both Blacks and Whites. However, Blacks had significantly lower anti-dyslipidemia medication use than Whites. The top three frequent anti-dyslipidemia medications were HMG-COA reductase inhibitors, fibric acid derivatives, and anti-hyperlipidemia combinations.

Conclusions: The significant differences in risk of cardiovascular disease in patients with T2DM are attributable to the differences in anti-diabetic and anti-dyslipidemia medication use in Blacks as compared with Whites.

266. Antipsychotic (AP) use in older adults with dementia: results from a post-authorisation safety study (PASS)

Deborah Layton,[1,2] Miranda Davies,[1,2] Vicki Osborne,[1,2] Saad AW Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK*

Background: The UK National Institute for Health and Care Excellence recommends that APs can be used in elderly patients (pts) under strict guidelines; however, use is associated with serious safety concerns (including cerebrovascular accidents (CVA)). Modified prescription-event monitoring (M-PEM) study was conducted as part of the Risk Management Plan for Seroquel XL© to examine safety and use as prescribed in primary care in England.

Objectives: The study is a *post hoc* analysis to examine the risk of CVA in the elderly.

Methods: M-PEM uses an observational cohort design; data on exposure were derived from dispensed prescriptions September 2008 to February2013; data on events from forms completed by physicians 12 months and aove (m) post each pt's start date. Age- and sex-adjusted (adj) Mantel–Haenszel odds ratios (ORs) and 95%CI were calculated for all cause deaths and CVA (MedDRA PT: CVA, cerebellar infarction, cerebral haemorrhage and haemorrhagic stroke) in elderly pts with/without dementia and with/without psychosis.

Results: Final elderly cohort is equal to 3127, median age 77 years (IQR 69,84) and 62% (1940) female; 892 (29%) had indications associated with dementia, of which 148 (17%) had concomitant psychosis. Within 12 months of starting Seroquel XL©, 10% (301) died, commonly from bronchopneumonia (44). Deaths were more likely in elderly with dementia than without [15% (136/892) vs 8% (165/2070); adjOR 1.5 [1.2, 1.9]] but not for dementia pts with psychosis vs those without [14% (21/148) vs 15% (115/744); adjOR 1.0 [0.6, 1.6]]. Twenty three (1%) had at least one report of CVA, 17 fatal. CVA events were twice as likely in pts with dementia than without [48% (11/23) vs 28% (881/3104); adjOR 2.8 [1.3, 6.2]].

Conclusions: Approximately one-third (29%) of this elderly cohort had dementia +/− psychosis. A higher

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rate of death was observed in elderly pts with dementia than without, but concomitant psychosis with dementia did not appear to be a risk factor. CVA was uncommon (<1%) but more likely in elderly with dementia than those without. Study limitations include low CVA counts, possible misclassification of depression and delirium as dementia and limited information on other possible factors (other modifiable medical and environmental factors).

267. Preadmission prescriptions of antidepressants and prognosis after colorectal cancer surgery

Kathrine D Lycke, Christian F Christiansen, Mette Nørgaard. *Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark*

Background: Cancer patients with psychiatric disorders have a higher mortality than non-psychiatric cancer patients.

Objectives: The study aimed to evaluate the association between prescription of antidepressants and outcome after colorectal cancer (CRC) surgery including intensive care unit (ICU) admission and 30-day mortality.

Methods: We conducted a population-based nationwide cohort study of all incident CRC patients who underwent surgery from 2005 to 2012 in Denmark. Exposure was defined as filling a prescription for antidepressants (ATC code N06A) within a year before surgery. We followed each patient for up to 30 days after surgery and estimated the cumulative incidence of ICU admissions (with death as a competing risk) and 30-day mortality. We constructed Kaplan–Meier survival curves and compared 30-day mortality using Cox proportional hazards regression with adjustment for age, gender, type of cancer and surgery, and somatic comorbidity.

Results: We identified 21 356 postoperative CRC patients, whereof 11.1% had a reimbursed prescription of antidepressants. Antidepressant users were older (mean age 72.7 vs. 69.9 years) and more often women (60.8% vs. 45.4%) and had higher prevalence of somatic comorbidity, especially cardiovascular (29.8% vs. 15.9%) and pulmonary diseases (20.8% vs. 12.6%), diabetes (14.4% vs. 10.8%) and dementia (4.8% vs. 0.8%). Additionally, users of antidepressants had a higher prevalence of colon cancer than non-users (73.6% vs. 68.0%) and were less likely to have undergone major surgery such as open or laparoscopic resection (86.9% vs. 90.0%). Within 30 days, 11.4% of antidepressant users were admitted to ICU compared with 7.9% among non-users (adjusted HR = 1.2; 95% CI [1.1, 1.4]). We found higher 30-day mortality among users of antidepressants than in non-users (10.5% vs. 5.2%, adjusted HR = 1.4; 95%CI [1.3, 1.7]).

Conclusions: CRC patients with a prescription of antidepressants have a higher ICU admission rate and 30-day mortality after surgery than non-users. Use of antidepressants and hereby underlying psychiatric disorder may therefore be considered a prognostic marker of CRC surgery outcome.

268. Survey on management of severe intensive care unit (ICU) infections: clinical experience with colistin methanesulfonate (CMS)

Chetan Mehndiratta, Pradip Gore, Mayuresh Fegade. *Ranbaxy Laboratories Limited, Mumbai, Maharashtra, India*

Background: There has recently been a tremendous increase in infections caused by multidrug-resistant (MDR) gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, and polymyxins (A, B, C, D and E) of which polymyxin B (PMB) and polymyxin E (colistin methanesulfonate) are often the only available active antibiotic. However, the factors associated with Colistin use and clinical outcomes have not been thoroughly examined.

Objectives: This survey was aimed to determine usage pattern, effectiveness and safety of colistin methanesulfonate in the management of severe ICU infections.

Methods: We conducted a retrospective cohort study conducted among patients prescribed colistin in intensive care units (surgical, medical or both) in India. The study was conducted from the clinical experience of 32 randomly selected physicians from all over India. Physician prescribers of colistin were provided with prescription event monitoring (PEM) forms that collected demographic and clinical variables including the type of infection treated, renal function status of patient's antibiotic susceptibility of organisms and perception on effectiveness of colistin by physician.

Results: Of the 285 patients having severe ICU infections, 61.76% were males, and 38.24 % were females. According to physicians perception, 91.58% of the patients were effectively managed with CMS. Most common indication for CMS therapy was sepsis (53.26%). Doripenem, imipenem + cilastin, meropenem, tigecycline, amikacin, combination of beta lactam + beta lactam inhibitors and cephalosporins were the most common concomitant medicines prescribed. Renal function was normal in 53.33% of patients admitted in ICU for severe infections. According to antibiotic sensitivity report, infections due to *E. coli* were most susceptible (94.39%) followed by *Acinetobacter baumannii* (82.43%).

Conclusions: Colistin methanesulfonate was perceived as effective by physician for management of severe ICU infections caused by multidrug-resistant gram-negative bacterial infections.

269. Survey on management of severe intensive care unit (ICU) infections: clinical experience with imipenem + cilastatin

Chetan Mehndiratta, Pradip Gore, Mayuresh Fegade. *Medical Services, Ranbaxy Laboratories Limited, Mumbai, Maharashtra, India*

Background: Imipenem + cilastatin is appropriately used for the sufficiently early for the treatment of severe nosocomial infections in the critically ill patient or in the critical care setting, particularly when no other antibiotic appears to be suitable or is available. Imipenem + cilastatin (Cilanem) was the first carbapenem antibiotic selected for development more than two decades ago because it was a highly potent, broad spectrum antimicrobial agent with a good safety profile.

Objectives: This survey was aimed to determine usage pattern, effectiveness and safety of imipenem + cilastatin in the management of severe ICU infections.

Methods: We conducted a retrospective cohort study conducted among patients prescribed imipenem + cilastatin in intensive care units (surgical, medical or both) in India. The study was conducted from the clinical experience of 52 randomly selected physicians across India. Physician prescribers of imipenem + cilastatin were provided with prescription event monitoring (PEM) forms, which collected demographic and clinical variables including the type of infection treated, renal function status of patient's antibiotic susceptibility of organisms and perception on effectiveness of imipenem + cilastatin by physician.

Results: Of the 666 patients having severe ICU infections, 61.76 % were males, and 38.24 % were females; average age in the study population was 51. 14 years. Physicians observed that 92.49% of the patients were effectively managed with imipenem + cilastatin. Most common indication for imipenem + cilastatin therapy was sepsis (35.27%), followed by complicated intra-abdominal infections (cIAI) in 24.43%. In cIAI, the most common indication for administration of imipenem + cilastatin combination was pancreatitis (30.19%). Renal function was normal in 50.91% of patients admitted in ICU for severe infections. According to antibiotic sensitivity report, infections due to *E. coli* were the most susceptible (94.65%) followed by *Klebsiella pneumoniae* (81.87%).

Conclusions: Imipenem + cilastatin combination was perceived as effective by physician for management of severe ICU infections caused by multi-drug-resistant gram-negative bacterial infections.

270. Prescription event monitoring of doripenem therapy in management of serious infections

Chetan Mehndiratta, Pradip Gore, Jejoe KaranKumar. *Medical Services, Ranbaxy Laboratories Limited, Mumbai, Maharashtra, India*

Background: Carbapenems are considered to be a mainstay of empirical therapy for hospitalized patients with serious infection. Doripenem, the newest agent in this class, was recently approved for the treatment of complicated intra-abdominal infections and complicated urinary tract infections. Several features and characteristics of doripenem broaden its antimicrobial spectrum beyond that of other carbapenems.

Objectives: This survey was aimed to determine the usage profile of doripenem and physician's clinical experience with it in the management of serious infections.

Methods: This survey was based on the clinical experience of 100 randomly selected physicians in the management of serious infections from different parts of India. Prescription event monitoring (PEM) forms comprising various questions were filled up

by these physicians. Data from 666 patients were analyzed.

Results: Five-hundred forty-eight patients having serious infection were admitted in intensive care unit (ICU) infections. The mean age in years of enrolled patiens was 52.27 of which 70.71% were males and 29.29% were females. The most common indication for doripenem is being sepsis (43.93%) and complicated intra-abdominal infections (cIAI) 25.63%. Of the cIAIs, peritonitis/anastomosis (24.81%) and pancreatitis (24.06%) were the most common indications; 55.56% patient had normal renal function and dose of 500 mg; 1-h infusion every 8 h was administered in 89.18% patients. *E. coli* (95.71%) and *Pseudomonas aeruginosa* (93.41%) were the most susceptible pathogens, whilst *Acinetobacter baumannii* (18.52%) and *Proteus mirabilis* (14.58%) were the most resistant forms; 92.78% patients were effectively managed with doripenem therapy.

Conclusions: Serious infections in ICU like sepsis and cIAI, due to *E. coli* and *Pseudomonas aeruginosa*, were effectively managed with doripenem therapy.

271. Effects of sex and alcohol use on antiretroviral therapy outcomes in Botswana

Robert Gross,[1] Scarlett L Bellamy,[2] Bakgaki Ratshaa,[3] Xiaoyan Han,[2] Andrew P Steenhoff,[3] Mosepele Mosepele,[4] Gregory P Bisson.[1] [1]*Medicine and Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA* [2]*Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA* [3]*Botswana-UPenn Partnership, Gaborone, Botswana* [4]*Massachusetts General Hospital, Boston, MA, USA*

Background: Gaps in the treatment continuum threaten the sustainability of antiretroviral therapy programs. Identifying the determinants of failure can inform intervention design.

Objectives: The study aimed to determine the rate and risk factors for failure during the initial 6 months of antiretroviral therapy in Botswana.

Methods: We conducted an observational cohort study in HIV-infected treatment naive adults >21 years old initiating efavirenz-based regimens in Botswana's national program. The primary outcome was a composite failure, which included death, loss to care, or plasma HIV RNA >50 copies/ml at month 6. Secondary outcomes were individual components of failure assessed separately. Exposure variables included demographics, the Alcohol Use Disorders Identification Test (AUDIT), and CD4 count and plasma HIV RNA at baseline. Adherence was assessed by medication refill.

Results: The 938 individuals included 478 (51%) male, median age 38 years (range 21–67), median baseline CD4 count 194 cells/mm^3 (110–252), and median baseline plasma HIV RNA 4.9 log10 copies/ml (4.2–5.4). Composite failure occurred in 339 (37%) including 40 (5%) deaths, 194 (21%) lost to care, and 105 (11%) with plasma HIV RNA >50 copies/ml. Male sex was the strongest risk factor for composite failure [adjusted OR 2.1 (95%CI [1.5, 2.9])] and loss to care [adjusted OR 2.1 (95%CI [1.3, 2.7])]. Hazardous alcohol use was more common among men than women (respectively, 51% vs. 19%, $p < 0.001$) and was associated with failure [adjusted OR 1.4 (95%CI [1.0, 1.9])] but did not mediate the relation between male sex and failure. Men who remained in care at 6 months were no more likely than women to be non-adherent or have HIV RNA >50 copies/ml.

Conclusions: Male sex and alcohol abuse conferred risk of failure, mostly from loss to care. Since alcohol abuse did not mediate failure in men, other modifiable factors need to be identified and targeted for intervention. Helping men remain in care is critical for antiretroviral programs in Botswana.

272. Systemic treatment of metachronous metastases after curative treatment of breast cancer

Josephina G Kuiper,[1] Myrthe PP van Herk-Sukel,[1] Yvette RBM van Gestel,[2] Adri C Voogd,[2,3] Valery EPP Lemmens,[2,4] Sabine Siesling.[5,6] [1]*PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands* [2]*Netherlands Comprehensive Cancer Organisation (IKNL), Eindhoven, The Netherlands* [3]*Department of Epidemiology, Maastricht University, Maastricht, The Netherlands* [4]*Department of Public Health, Erasmus MC University Medical Centre, Rotterdam, The Netherlands* [5]*Department of Health Technology and Services Research, University of Twente, Enschede, The Netherlands* [6]*Netherlands*

Comprehensive Cancer Organisation (IKNL), Enschede, The Netherlands

Background: Approximately 20% of breast cancer patients initially diagnosed with non-metastasized disease develop metachronous metastases. Data on systemic treatment of metachronous metastases were scarce.

Objectives: The study aimed to describe the systemic treatment of metachronous metastases and the reasons of not receiving systemic treatment in patients with breast cancer.

Methods: Patients diagnosed with M0 breast cancer at initial diagnosis between 2006 and 2008 were selected from the Eindhoven Cancer Registry. By means of an active follow-up until January 2012, data on development of metastatic disease, treatment and reasons of not receiving systemic treatment were collected directly from the patient files.

Results: Of the 1382 patients diagnosed with M0 breast cancer, 116 (8%) developed metachronous metastases during a median follow-up of 4.4 years. Of the patients developing metachronous metastases, 86 (74%) patients received systemic treatment with a median (±SD) age of 59.7 (±13.4) years. Of these, 46 patients (53%) received chemotherapy, 19 patients (22%) received hormonal therapy and 21 patients (24%) received a combination of chemotherapy and hormonal therapy. Median (±SD) age of patients who did not receive systemic treatment ($n = 30$) was 70.0 (±15.9) years. Of the 67 patients receiving chemotherapy, 17 patients (25%) were treated with taxane containing chemotherapy as first-line treatment. Of the 30 patients without any systemic treatment, 10 patients received radiotherapy, three patients underwent surgery and six patients refrained from systemic treatment. Other reasons for not receiving systemic treatment were extensiveness of metastases ($n = 4$), death before first application of chemotherapy ($n = 4$), high age ($n = 1$), comorbidities ($n = 1$) or bad experience with chemotherapy in the past ($n = 1$).

Conclusions: Of the initially M0 breast cancer patients developing metachronous metastases, the majority received systemic treatment. A quarter of the patients did not receive systemic treatment due to other treatment policies, refraining from treatment or poor condition. This study provides more insight into the treatment of metachronous metastases in the Netherlands.

273. Generic and essential medicines towards a more efficient use of resources in the prevention and treatment of cardiovascular diseases in Portugal

Helena Gama,[1] Carla Torre,[2] Jose Pedro Guerreiro,[2] Maria João Lima,[3] Ana Azevedo,[1,4] Suzete Costa,[2] Nuno Lunet.[1,4] *[1]Institute of Public Health of the University of Porto (ISPUP), Porto, Portugal [2]Centre for Health Evaluation and Research (CEFAR), National Association of Pharmacies Group, Lisboa, Portugal [3]Department of Internal Medicine, Centro Hospitalar São João, Porto, Portugal [4]Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal*

Background: The successful control of cardiovascular diseases at the lowest possible cost requires the use of the most effective and affordable medicines.

Objectives: We aimed to describe the trends in the ambulatory use of medicines for prevention and treatment of cardiovascular diseases in Portugal, between 2004 and 2012, and to estimate the potential for expenditure reduction through changes in the patterns of use.

Methods: Drug consumption data [Anatomic Therapeutic Chemical classification system: C and B01A] were estimated for the study period through the CEFAR Pharmacy Sales Information System, a nationwide database with representative drug dispensing data from ambulatory care. Main outcome measure was the defined daily dose (DDD) per 1000 inhabitants per day (DHD). Total costs in euro and the cost/DDD were calculated based on pharmacy retail price (€).We estimated the potential reduction in expenditures through the increase, up to 90% of the volume of DDD, in the use of generic and essential medicines; the latter were defined according to the guidelines from Portugal and another European country.

Results: The overall consumption increased by approximately 50% from 2004 to 2012, reaching nearly 2400 million DDD, whereas the expenditure decreased to 753 million € (–31.3% since 2006). The use of generics and essential medicines increased, representing 43.6% and 36.1% of the DDD consumption in 2012, respectively. The 40 most used groups of medicines in 2012 accounted for just over 80% of the overall consumption; among these, the increase in the use of generics and essential medicines would

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have contributed to a saving of 70 and 200 million €, respectively.

Conclusions: Changes in the patterns of consumption of medicines towards a preferential use of essential medicines may contribute to a more efficient use of health resources, adding to the already high use of generics.

274. Patients' awareness of bioequivalence study methods supporting generic venlafaxine extended release (ER) tablet approval

Bilal Khokhar,[1] Yujin Park,[1] Francoise Pradel,[1] Francis Palumbo,[1] Zippora Kiptanui,[2] Sarah Dutcher,[3] Wenlei Jiang,[3] Ilene Zuckerman.[2] *[1]Pharmaceutical Health Services Researcher, University of Maryland Baltimore, Baltimore, MD, USA [2]IMPAQ Internationl, Columbia, MD, USA [3]FDA, Silver Spring, MD, USA*

Background: Generic venlafaxine ER tablet was approved by the FDA using an alternative approval method, as it relied on a fed bioequivalence test only.

Objectives: The study aims were as follows: (1) to assess patients' awareness that a fasting bioequivalence study was not recommended for generic venlafaxine ER tablet and (2) to test whether knowledge of this approval method influences patients' perceptions of generic venlafaxine ER tablet.

Methods: A web-based survey was created and disseminated to multiple Facebook groups and to members of PatientsLikeMe®. Past and/or current users of venlafaxine ER tablets were eligible for this survey. Descriptive statistics were calculated, and a paired *t*-test was used to determine differences in patient perceptions of generic venlfaxine ER tablets prior to and following knowledge of the alternative method used to approve generic venlafaxine ER tablets.

Results: Of the 218 patients who accessed the survey, 170 were disqualified for various reasons, mainly for taking venlafaxine ER capsules rather than tablets (79%). Of the remaining 48 qualified patients, 31 patients completed the survey, while 17 left the survey incomplete. Most patients were female (65%) and White (94%). Almost all patients (90%) were not aware of the bioequivalence method used for generic venlafaxine ER tablet. Participants were less comfortable with taking generic tablets after receiving information that a fasting bioequivalence study was not evaluated for generic venlafaxine ER tablet approval, compared with before receiving the information (64% versus 74%, $p = 0.018$).

Conclusions: Although most patients were unaware of the non-traditional bioequivalence approach used to approve generic venlafaxine ER tablet, many were not comfortable with this approach once informed. These preliminary findings may be useful to the FDA in communicating with and educating the public regarding generic drug approval processes in order to improve patients' comfort level with generic drugs.

275. Prescribing pattern of anti-epileptic and concomitant drugs in children with epilepsy in India

Anil Dasari,[1] Dipika Bhansal,[1] Chandrika Azad.[2] *[1]National Institute of Pharmaceutical Education and Research, SAS Nagar, India [2]Government Medical College and Hospital, Chandigarh, India*

Background: Anti-epileptic drugs (AEDs) are the drugs with considerable intervariability and are susceptible to cause adverse drug effects and drug interactions. Amongst various factors affecting anti-epileptic drug prescription, the availability and affordability as well as place of practice and choice of treating physicians are the most important. Investigation of prescription patterns and exposure of AEDs to different patient groups are important regarding drug safety aspects. More research studies are required in this area due to lack of well-defined evidence in India to conclude.

Objectives: The aim of the study is to investigate the prescribing pattern of AEDs and concomitant medications (CMs) in children with epilepsy.

Methods: It is an observational cohort study conducted in the outpatient daportment of public tertiary care hospital, Chandigarh, India. Children were enrolled in the study if they are between 1–18 years and were diagnosed with idiopathic or symptomatic epilepsy and on AED treatment for at least 3 months. Relevant data regarding demographics, disease and medication details were collected from patient medical records and by structured patient interview.

Results: A total of 377 epileptic children were included in this study. Amongst the included children, 60% were boys and had mean age of 8 (SD, 4) years. Most commonly prescribed AEDs were phenytoin (66%), valproic acid (44%), carbamazepine (22%) and others. Newer drugs like clonazepam, clobazam, levetiracetam and tegretol were prescribed only in 8%, 5%, 1% and 1% of children, respectively. Lamotrigine was prescribed only in one children. Eighty-nine percent children were on monotherapy. Average number of AEDs prescribed per child was 1.5. Most commonly prescribed CMs were found to be calcium, folic acid, vitamin D, albendazole and prednisolone.

Conclusions: Most commonly prescribed AEDs were conventional type; only 16% children were prescribed newer epileptics. Commonly prescribed CMs were found to be calcium, folic acid and vitamin D.

276. Socio-demographic and geographic variations in the utilization of hormone therapy in older breast cancer women with Medicare Part-D coverage

Xin Wang,[1] Xianglin Du.[2] *[1]Pharmaceutical Health Outcomes and Policy, College of Pharmacy, University of Houston, Houston, TX, USA [2]Department of Epidemiology, Human Genetics, and Environmental Sciences, University of Texas School of Public Health, Houston, TX, USA*

Background: Adjuvant hormonal therapy has been recommended for patients with hormone receptor (HR)-positive early stage breast cancer after definitive surgery.

Objectives: The study aims were to assess social demographic, geographical, and other variations in the receipt of hormonal therapy among hormone-receptor positive breast cancer patients and to assess compliance to hormonal therapy within a 1-year follow-up.

Methods: A retrospective cohort study was conducted using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data in 2006–2009. Percentage of hormone-receptor positive breast cancer patients who received hormone therapy was calculated by each month, stratified by chemotherapy status (yes or no). Three multivariate logistic regression models were performed to assess variations associated with the use of hormone therapy, selective estrogen receptor modulators (SERMs), and aromatase inhibitors (AIs), respectively. The models were adjusted for age, gender, race, marriage status, SEER registry area, year of diagnosis, tumor stage, tumor size, radiation status, surgery status, and comorbidity.

Results: Of the 25 128 women with hormone receptor positive breast cancer in 2006–2009 who were enrolled in Medicare Part-D program, 70.8% received hormone therapy, 22.2% received SERM, and 56.9% received AIs. Among those receiving chemotherapy, significant predictors of receiving hormone therapy included age, tumor stage, surgery type, and radiation therapy; significant predictors of receiving SERM included race, year of diagnosis, and tumor stage; significant predictors of receiving AI included age, race, social economic status, geographic location, tumor stage, and radiation therapy. For those without receiving chemotherapy, most of the above factors were significant but differed across each drug class.

Conclusions: Over two-thirds of hormone-receptor positive breast cancer patients received hormonal therapy. Tumor and clinical factors are the most significant predictors for the receipt of hormone therapy. The underlying reasons for the differences in those significant factors affecting the receipt of AIs versus SERM need to be further investigated.

277. Polypharmacy and multiple indications among adults prescribed antidepressants

Jenna Wong,[1] Aude Motulsky,[2] Robyn Tamblyn.[1] *[1]Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada [2]Faculty of Medicine, McGill University, Montreal, QC, Canada*

Background: An increasing number of patients are concurrently taking multiple antidepressants. However, the prevalence of polypharmacy with antidepressants and the extent to which it occurs to optimize treatment outcomes for a single indication or to treat multiple indications is unknown.

Objectives: The study aimed to determine the prevalence of polypharmacy with antidepressants and the frequency with which antidepressants are prescribed for multiple indications.

Methods: This is a descriptive study of adult prescriptions for SSRIs, SNRIs, TCAs, MAOIs and other

antidepressants (e.g. bupropion, mirtazapine and trazodone) written by general practioners between January 2003 and December 2012 using an electronic prescribing system in Canada. Adults were followed from the date of their first antidepressant prescription until the earliest of death or December 2012. Prescription indications were mandatorily obtained from physicians at the time of prescribing via a drop-down menu or free-text field. Prescriptions were considered active from the issue date until the expiry date or until the physician stopped the prescription.

Results: A total of 17 622 adults were prescribed at least one antidepressant and followed for a median of 4.6 (IQR 2.5–6.4) years. The median treatment duration with a drug was 10.2 (IQR 5.5–13.0) months. At any point, 3842 (22%) adults were concurrently prescribed different antidepressants, of whom 3551 (92%) were prescribed drugs from different therapeutic classes, 724 (19%) were prescribed drugs within the same class and 2471 (64%) were prescribed drugs for different indications. The most common drug combinations were trazodone with venlafaxine (11%) or citalopram (10%), and the most common class combinations were other antidepressants with SSRIs (46%) or SNRIs (27%). The most common indication combinations were depression and sleep disorders (39%) and depression and anxiety (22%).

Conclusions: We found that approximately one in five adults seen in primary care is concurrently prescribed multiple antidepressants, often to treat different medical conditions.

278. Role of residential segregation in disparity research: a case example of ADHD diagnosis and treatment

Dinci Pennap, Mehmet Burcu, Julie M Zito. *Pharmaceutical Health Services Research, University of Maryland, Baltimore, MD, USA*

Background: Geographic and racial/ethnic variations in the diagnosis and treatment of ADHD have been extensively studied. However, little is known about the role of residential segregation in understanding racial/ethnic disparities in health services utilization (HSU) among ADHD-diagnosed youth.

Objectives: The study aimed to characterize practice patterns of HSU according to region and race/ethnicity and to assess residential segregation as an effect modifier in the racial/ethnic disparities in the diagnosis and treatment of ADHD.

Methods: A cross-sectional design was applied to US Pacific state Medicaid claims linked to U.S Census Bureau data on zip code level population statistics. At least two outpatient ADHD claims on separate visit days were required to qualify as a diagnosed ADHD visit. Hispanic residential segregation (HRS) was defined as the proportion of the Hispanic population in enrollees' zip code of residence and categorized as $<15\%$, 15.0–29.9%, 30.0–44.9%, and $\geq 45\%$. We assessed regional and race/ethnic differences in ADHD diagnosis and stimulant use, adjusting for other sociodemographic and clinical characteristics. In a second set of regression models, we included interaction terms between HRS level and race/ethnicity to examine the role of HRS on disparities in ADHD diagnosis and treatment.

Results: The study population was largely of Hispanic ethnicity (63.7%) and resided predominantly in highly segregated neighborhood (at least 45% Hispanic residents). The prevalence of ADHD diagnosis varied significantly by region ranging from 1.8% to 4.6% and ranged from a low of 1.2% for Hispanic youth to a high of 5.0% for White youth. Among the ADHD-diagnosed youth, 59.8% received at least one stimulant dispensing in 2009 with significant variation in use by race/ethnicity and region. The Hispanic to White disparity intensified with increasing HRS for both ADHD diagnosis and stimulant use.

Conclusions: Residential segregation (RS) intensifies racial/ethnic disparities in health service use in ADHD-diagnosed youth. RS research should be pursued to corroborate these findings and expand the framework for pharmacoepidemiology research.

279. Socioeconomic differential in 1-year survival after hospitalization for ischemic stroke: the effect of acute and post-acute care pathways

Valeria Belleudi, Paolo Sciattella, Nera Agabiti, Mirko Di Martino, Riccardo Di Domenicantonio, Marina Davoli, Danilo Fusco. *Department of Epidemiology, Lazio Regional Health Service, Rome, Italy*

Background: Low socioeconomic is associated with increased stroke mortality after hospitalization. The role of care pathway in survival inequity is not known.

Objectives: The aim of the study was to explore the role of ischemic stroke care pathway on the association between education level and 1-year survival.

Methods: From Lazio health data warehouse, a cohort of incident hospitalizations for ischemic stroke in adults during 2011/2012 was selected. For each subject, the clinical history was reconstructed through previous hospitalizations and drug prescriptions. The association between education level and mortality was studied for acute (2–30 days from admission) and post-acute phase (31–365 days from discharge) using multivariate logistic and Cox models. To identify the different care pathway scenarios, we considered hospital performance (in terms of mortality) for acute phase and drug treatment post-discharge (number of drugs among antihypertensive, antithrombotic and statins) for post-acute phase. The probability to survive to acute and post-acute phases according to education level and care pathway scenarios was estimated for a 'mean severity' patient (same distribution of comorbidities of the cohort). One-year survival probability was calculated as the product of two probabilities. For each scenario, 1-year probability ratio, university versus elementary and its Bayesian confidence intervals [BCI95%] were calculated.

Results: We identified 9958 patients with ischemic stroke (mean age = 76 years; 50% male), 53.3% with elementary and 3.2% with university. The mortality was 14.9% in acute phase and 15.7 per 100 p.y. in post-acute phase among survivors. The adjusted mortality rates in acute and post-acute phase decreased with the increase of educational level (RR = 0.90 p-trend < 0.001; HR = 0.85 p-trend < 0.001). For the best care pathway (hospital with high performance, use of all three drugs), the 1-year probability rate university vs elementary was 1.05 [1.03, 1.08], while was 1.22 [1.12, 1.32] for the worst.

Conclusions: Patients with the best care pathway had a higher 1-year probability to survive. The care pathway reduces but not eliminates survival inequity.

280. Drug utilization study of asthma medications in the U.S. Medicare beneficiaries

Ayad K Ali. *Eli Lilly and Company, Indianapolis, IN, USA*

Background: Asthma is a chronic respiratory inflammatory disease that is increasing in prevalence and burdens; however, it is under-diagnosed and under-treated in the elderly. Although clinical consequences of asthma in the elderly can be similar to those in younger patients, the presence of comorbidities influences treatment choice in older patients, and the utilization of asthma medications is not well characterized in the elderly.

Objectives: This study describes the utilization of asthma treatments during 12 months of asthma diagnosis in adults 50 years and older.

Methods: Patients diagnosed with asthma and enrolled in U.S. Medicare are followed for a maximum of 12 months after first asthma diagnosis. Patients with a history of chronic obstructive pulmonary disease are excluded. Medication classes are identified using the National Drug Codes. Treatment pattern analysis was limited to new drug initiators. At least one prescription is required for therapy switch or augmentation following exposure to first-line therapy.

Results: Between 2004 and 2012, there were 126 176 patients with asthma; of those, 24 021 initiated asthma therapy within 12 months of asthma diagnosis. Seventy percent were females with a median age of 70 years. Fifty-eight percent of started medications were discontinued during the analysis period, 26% were augmented with, and 14% were switched to another asthma treatment. Most patients initiated rescue inhalation therapy with short-acting beta-agonists (SABA); majority of them discontinued SABA or added another asthma therapy. Nineteen percent of patients started oral corticosteroids after asthma diagnosis, but most of them discontinued therapy and switched to another asthma controller medication. Inhaled corticosteroids (ICS), ICS/long-acting beta-agonists, and leukotriene antagonists contributed to 12%, 19%, and 11% of treatment initiators, respectively. The majority of these controller medications were replaced or augmented with another asthma medication.

Conclusions: Initiation of anti-inflammatory asthma therapy in newly diagnosed elderly patients appears to be inconsistent with current asthma management guidelines, and treatment patterns reflect poor asthma control among this population.

281. Misclassification of indication when measuring indacaterol use in a US administrative claims database

Scott C Quinlan,[1] Rajeev K Amar,[2] Raymond Schlienger,[2] Stephan Lanes,[1] Crystal N Holick.[1] [1]*Safety and Epidemiology, HealthCore, Inc.,*

Wilmington, DE, USA [2]Drug Safety and Epidemiology, Novartis Pharma AG, Basel, Switzerland

Background: Arcapta™ Neohaler™ (indacaterol 75 mcg [IND]; Novartis Pharma AG) is a long-acting beta-2-agonist approved by the United States Food and Drug Administration in 2011 for maintenance treatment of chronic obstructive pulmonary disease (COPD). As part of Novartis's risk management plan (RMP), a post-marketing, observational study is being conducted to evaluate IND usage in a real-world setting.

Objectives: The study aimed to monitor the effectiveness of the IND RMP in deterring prescribing for non-approved indications.

Methods: We conducted a cohort study of IND initiators using secondary data from the HealthCore Integrated Research Database (HIRD). Medical and pharmacy claims on or before the first IND dispensing date defined COPD/asthma history and concomitant inhaled corticosteroid (ICS) therapy. Off-label use included users with asthma alone or mixed disease (COPD and asthma) without concomitant ICS therapy. For the primary interim analysis, COPD/asthma history was defined by ≥1 diagnosis. Sensitivity analyses examined different COPD and asthma definitions. Diagnoses were identified in the claims only and not validated in medical records.

Results: An interim analysis identified 205 IND users between March 2012 and November 2013, of whom 54 (26.3%) were classified as off-label users (17 with asthma alone and 37 with mixed disease without ICS therapy) using ≥1 diagnosis to define COPD/asthma history. Requiring ≥2 diagnoses classified 21.5% as off-label use. Using the latest diagnosis on or prior to IND initiation, off-label use decreased to 20.0%.

Conclusions: Sensitivity analyses showed that classification of disease history depends on coding algorithms. Sensitive algorithms for COPD/asthma history likely introduced misclassification of indication for IND treatment, which accounted for some of the apparent off-label prescribing. More specific definitions of COPD/asthma history appeared to reduce the misclassification of indication.

282. Prescribed opioid use and potential misuse in Australia (2006 to 2013)

Bianca Blanch,[1] Nicholas A Buckley,[2] Preeyaporn Srasuebkul,[1] Melisa Litchfield,[1] Sallie-Anne Pearson.[1]

[1]Pharmacoepidemiology and Pharmaceutical Policy Research Group, Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia; [2]School of Pharmacology, University of Sydney, Sydney, NSW, Australia.

Background: Prescribed opioid misuse is increasing globally, yet there is limited research quantifying the extent of the problem in an Australian population. 'Doctor shopping' is the most commonly used proxy of prescribed opioid misuse applied in routine data collections.

Objectives: To estimate rates of opioid use and potential misuse in Australia from 2006 to 2013.

Methods: Australian citizens and permanent residents access subsidised prescribed medicines under the Pharmaceutical Benefits Scheme (PBS). We used a dataset comprising the dispensing history of a random 10% sample of PBS beneficiaries. Our eight annual (calendar year) cohorts included: adults (aged ≥18 years on January 1), ≥1 dispensing(s) of a PBS-reimbursed medicine and beneficiaries for whom we have complete medicine ascertainment (representing between 54%-62% of medicine users annually). We estimate potential misuse based on 'doctor shopping', ≥5 prescribers for opioids per calendar year. We report the rate of opioid use and misuse per 1000 beneficiaries.

Results: Overall, opioid utilisation increased from 232.7 to 262.4 but remained relatively constant between 2008–2009 and 2012–2013. Rates of potential misuse increased annually from 6.3 to 10.4. 'Misusers' were dispensed 14.7–15.4% of all opioids every year. In all users, oxycodone and codeine/paracetamol combinations were the most commonly dispensed opioids across all years. In potential misusers, oxycodone accounted for 28.1% of all opioid dispensings in 2006 and 43.4% in 2013, an increase of 54.4%. In contrast, codeine/paracetamol combinations accounted for 29.9% of all opioid dispensings to potential misusers in 2006 and 17.3% in 2013, a decrease of 42.1%.

Assuming the same rates of misuse across all Australians as in this study cohort, we estimate approximately 93 898 doctor shoppers in Australia in 2013.

Conclusions: In Australia, rates of opioid use have increased, and rates of potential misuse (measured by our sole proxy) have increased annually since 2006.

Doctor shoppers accessed a significant proportion of all opioids dispensed annually. The challenge for policy makers is to develop interventions to curb misuse without reducing opioid access for legitimate opioid users.

283. Quality of community pharmacy care in the Netherlands: changes in dispensing outcome scores across 5 years

Martina Teichert,[1,2] Tim Scheonmakers,[1] Nico Kijlstra,[3] Berend Mosk,[4] Marcel Bouvy,[5,6] Frans van de Vaart,[2] Peter de Smet,[1,2] Michel Wensing.[1]
[1]Radboud Institute for Health Sciences, Department of IQ Healthcare, Radboud University Medical Centre, Nijmegen, the Netherlands [2]Research and Development, Royal Dutch Pharmacists Associciation, KNMP, The Hague, the Netherlands [3]Healthcare Inspectorate, Utrecht, the Netherlands [4]National Health Care Institue, Diemen, the Netherlands [5]SIR Institute for Pharmacy Practice and Policy, Leiden, the Netherlands [6]Pharmacoepidemiology and Clincial Pharmacology, Department of Pharmceutical Sciences, Utrecht University, Utrecht, the Netherlands

Background: Since 2008, data on a comprehensive quality indicator (QI) set were collected annually from all Dutch community pharmacies. On four dispensing outcome QIs, information was available for 5 years: suboptimal combination of coumarins with co-trimoxazol and advised protective co-medication for nitrates, opioides and elderly NSAID users. From 2009, pharmacies received annually feedback reports with information on national scores. As of 2010, health insurance companies used QI scores for pay-for-performance contracts.

Objectives: The study aimed to describe the magnitude of differences in QI scores between subsequent years within individual pharmacies for dispensing outcome QIs measured between 2008 and 2012.

Methods: In a cross-sectional design, the four QIs were calculated by drug dispensing data on an individual community pharmacy level. Differences on QI scores were calculated by subtracting the scores of the preceding year from the annual pharmacies scores. The four resulting differences were clustered for high changes (≥5%), low changes (1–5%) and almost no changes (zero −1%).

Results: Data of 1739 pharmacies (88% of all Dutch community pharmacies) were available. The highest improvements of the scores on the four dispensing outcome QIs were seen between the first two study years:45% of all Dutch community pharmacies had a decrease in number of subjects with the coumarin interaction of at least 1%; protective co-mediction increased by >1% for NSAID users (80% of all pharmacies), nitrate users (76%) and opoid users (79%). As of 2011, the maximum scores to be achieved in daily practice seemed to be reached.

Conclusions: Feedback reports may have stimulated QI score improvement within the first 2 years.

Pay-for-performance policies of health insurance companies may have contributed to further improvement. To stimulate further progress, QIs that achieved maximum scores in daily practice or seem to depend on additional factors outside pharmaceutical care performance should be replaced by new aspects.

284. Effect of a certified quality management system on dispensing outcome quality indicators in community pharmacies

Martina Teichert,[1,2] Tim Schoenmakers,[2] Nico Kijlstra,[3] Berend Mosk,[4] Marcel Bouvy,[5,6] Frans van de Vaart,[1] Peter de Smet,[1,2] Michel Wensing.[2]
[1]Reserach and Development, Royal Dutch Pharmacists Association, KNMP, The Hague, The Netherlands [2]Radboud Institute for Health Sciences, IQ Healthcare, Radboud University Medical Centre, Nijmegen, The Netherlands [3]Healthcare Inspectorate, Utrecht, The Netherlands [4]National Health Care Institue, Diemen, The Netherlands [5]SIR Institute for Pharmacy Practice and Policy, Leiden, The Netherlands [6]Pharmacoepidemiology and Clincial Pharmacology, Department of Pharmceutical Sciences, Utrecht University, Utrecht, The Netherlands

Background: A comprehensive quality indicator (QI) set with structure, process and dispensing outcome QIs was measured annually in Dutch community pharmacies.

Objectives: The study aimed to explore the impact of relevant structures and processes as testified by a certified quality management system (QMS) on the score development of dispensing outcome QIs in community pharmacies between 2008 and 2012.

Methods: Annual data were available QI scores. Outcome QIs addressed the number of coumarin users

with concomitant co-trimoxazol treatment and the percentages of NSAID users above 70 years old with gastroprotection, nitrate users with antithrombotics and opioide users with laxatives during a calendar year.

Multivariate linear mixed models were used to analyse the association of a QMS on score development of the outcome QIs within individual pharmacies.

Results: Data of 1739 pharmacies (88% of all Dutch community pharmacies) were available.

Percentages of NSAID users with concomitant gastroproection increased from a mean of 70.8% in 2008 to 84.7% in 2012. A QMS was significantly associated with this development, beta 2.17 (95%CI [1.59, 2.76]).

Percentages of nitrate users with antithrombotic prevention increased from a mean of 75.8% in 2008 to 93.0% in 2012. A QMS was significantly associated with this development, beta 1.98 (95%CI [1.31, 2.64]), and a significant multiplicative interaction ($p < 0.05$).

Percentages of opioid users with concomitant laxatives increased from a mean 44.5% in 2008 to 54.1% in 2012. A QMS was not significantly associated with this development, beta 0.59 (95%CI [−0.21, 1.39). The number of coumarin users with the unfavourable interaction decreased from a mean of 18 patients per community pharmacy in 2008 to a mean of 0.7 in 2012. This decrease was not associated with a QMS, beta −0.65 (95%CI [−4.01, 2.73]).

Conclusions: A QMS was significantly associated with QI scores on preventive co-mediation with NSAIDs and nitrates. Other parameters than pharmacy structures and processes seemed to have influenced the decrease of coumarin interactions and the scores for opioids in combination with laxatives.

285. Translation and cross-cultural adaptation of the brief illness perception questionnaire, the beliefs about medicines questionnaire and the Morisky Medication Adherence Scale into Vietnamese

Thang Nguyen,[1,2] Thao H Nguyen,[3] Suol T Pham,[1] Hoang TK Cao,[1] Khanh K Le,[1] Hoa TK Pham,[4] Phong T Pham,[5] Dung N Quach,[1] Dao TT Tran,[1] Tam T Pham,[6] Katja Taxis.[2] *[1]Department of Pharmacology and Clinical Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam; [2]Department of Pharmacy, Unit of Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands [3]Department of Clinical Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh city, Ho Chi Minh City, Vietnam [4]Department of Cardiology, Can Tho General Hospital, Can Tho, Vietnam [5]Department of Cardiology, Can Tho Centrsl General Hospital, Can Tho, Vietnam [6]Faculty of Public Health, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam*

Background: Little is known about illness perceptions, beliefs about medicines and medication adherence of patients with chronic diseases in Vietnam.

Objectives: The objectives were to translate and cross-culturally adapt the Brief Illness Perception Questionnaire (BIPQ), the Beliefs about Medicines Questionnaire (BMQ) and the Morisky Medication Adherence Scale-eight items, (MMAS) into Vietnamese.

Methods: We followed the five stages of the guideline by Beaton *et al* (2000): Stage I, two forward translators (informed and uninformed) translated the questionnaires; Stage II, the translations were synthesized; Stage III, back translation was performed by two translators naive to outcome measurement; Stage IV, six experts (two translators, two physicians and two researchers) reached consensus on pre-final Vietnamese version; and Stage V, field test of the questionnaires in acute coronary syndrome (ACS) patients from one Vietnamese hospital.

Results: Three out of 35 items were difficult to translate. One example was the BMQ item 'My medicines are a mystery to me', which had to be modified as 'I do not understand my medicines completely' as there was no suitable word for 'mystery' in Vietnamese. Thirty-one patients completed the questionnaires and were interviewed (mean age 65.5 years and 81% male). There were two questionnaire items misunderstood: BIPQ 5 (two patients) and MMAS 5 (one patient). For instance, the MMAS 5 'Did you take all your medicine yesterday' was misunderstood as 'Did you take the whole supply of your medicines yesterday'. Means (standard deviations) of BIPQ composite score, the Necessity, Concerns, Overuse and Harm subscales of the BMQ were 6.8 (0.9), 24.5 (2.8), 16.9 (5.8), 12.7 (3.0) and 10.6 (3.7), respectively. There were 45% ACS patients with high adherence to prescribed medications (MMAS score = 8), 32%

medium adherence (MMAS score = 6 or 7) and 23% low adherence (MMAS score <6).

Conclusions: We obtained cross-culturally adapted Vietnamese versions of the BIPQ, BMQ and MMAS. Additional work is needed to test the retention of the psychometric properties of the adapted questionnaires.

286. Access to drug benefit plans among Canadian cancer survivors

Lawson Eng,[1] Devon Alton,[2] Tom Yoannidis,[3] Robin Milne,[4] Samantha Sarabia,[4] Zahra Merali,[4] Liam Murphy,[4] M Catherine Brown,[4] Ashlee Vennettilli,[4] Meredith E Giuliani,[2] Wei Xu,[5] Geoffrey Liu.[1] *[1]Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada [2]Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada [3]Wharton Head and Neck Program, Princess Margaret Cancer Centre, Toronto, ON, Canada [4]Applied Molecular Oncology, Princess Margaret Cancer Centre/Ontario Cancer Institute, Toronto, ON, Canada [5]Department of Biostatistics, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Advances in the early detection of cancer and cancer therapies have led to improvements in the length and quality of life of cancer patients. However, patients may require access to supportive medications or services not routinely available through general government healthcare coverage but through drug benefit plans. Understanding the patients who have such access may guide healthcare providers to provide additional disparity research.

Objectives: The study aimed to identify cancer patients who have access to drug benefit plans.

Methods: Lung and head and neck (HN) cancer patients from a tertiary cancer centre, Princess Margaret Cancer Centre (Toronto, Canada), completed a questionnaire assessing socio-demographics and whether they had a drug benefit plan. Multivariate logistic regression models evaluated the association of socio-demographic and clinicopathological variables with whether patients had a drug benefit plan.

Results: Among the 295 patients, 52% had HN cancer; 41% were over 65 years of age; 85% of patients received curative therapy. Seventy-three percent (72% lung and 73% HN; 77% less than 65 years of age and 69% 65 years or older) reported having a drug benefit plan. Univariate analysis found that patients who were younger ($p = 0.03$), employed ($p = 0.009$), having a higher household income ($p = 0.03$), not receiving radiation therapy ($p = 0.01$) and receiving any therapy ($p = 0.03$) were more likely to have a drug benefit plan. Multivariate analysis found younger patients (aOR = 0.97 per 1-year increase; 95%CI [0.94, 0.99], $p = 0.03$) and those not receiving radiation therapy (aOR = 2.47 [1.13, 5.47], $p = 0.02$) were being more likely to have a drug benefit plan. Subgroup analysis by disease site revealed that in lung cancer, younger patients (aOR = 0.96 [0.92, 0.99], $p = 0.02$) were more likely to have a drug benefit plan and in HN cancer, there was a trend towards patients with higher household income having a drug benefit plan (aOR = 2.70 [0.98, 7.14], $p = 0.06$).

Conclusions: Most lung and HN cancer patients have access to a drug benefit plan. Older cancer patients and those receiving radiation therapy may need attention at helping to ensure they have access to such plans. Additional data on other cancer disease sites will be presented at the meeting.

287. Affordability of medicines in Armenia

Irina Kazaryan,[1] Anahit Sevikyan,[2] Margarit Melikyan,[1] Anahit Amirkhanyan.[2] *[1]Drug Utilization Research Group PO, Yerevan, Armenia [2]Yerevan State Medical University, Yerevan, Armenia*

Background: Reimbursement system in Armenia covers only medicines for patients from certain vulnerable groups (some social groups and patients with certain diseases); correspondingly, the majority of patents are forced to purchase medicines out of pocket. As income of many households is quite low, medicines are not always affordable for patients.

Objectives: The objective of this study was to assess the cost of treatment for patients with some widespread diseases (adult respiratory infection, hypertension, diabetes, asthma and so forth).

Methods: Data on prices for more than 50 medicines were collected for June and December of 2009 and 2010, respectively, from 30 community pharmacies

located in different regions of Yerevan (capital of Armenia). Affordability of medicines was calculated based on methodology developed by Health World Organization (WHO) and Health Action International (HAI).

Results: Despite price fluctuations, which were observed for some medicines, prices of the majority of pharmaceuticals selected for the study increased from June 2009 to December 2010, during this period. Prices have increased by 25% and more for such products as Unidox Solutab, Corinfar retard, Adalat retard and Ciprobay. A large difference in the affordability of originator brand products (and brand name generics) and the lowest-priced generics was observed. The number of days the worker with the approval by the government minimal salary needs to work in order to be able to pay for a standard course of treatment for Asthma (salbutamol, one inhaler of 200 doses) was 2.8 if originator brand product is used and 0.85 for the lowest-priced generic. The originator brand product of amitriptyline was not available, but the number of days for worker with the minimal salary to work in order to pay for treatment of depression with the lowest-priced generic (25-mg capsule or tablet, three times daily, a 30-day course) was about 1.7.

Conclusions: Treatment of some diseases is not always affordable, especially taking into account that brand products are mainly prescribed by physicians and selected by patients. Introducing price regulation and/or other strategies intended for reducing medicine prices could be useful for improving the situation.

288. Drug utilization: pattern and influence on the quality of life of patients under care at public health centres in Brazil

Katia Rodrigues Silva, Micheline Rosa Silveira, Celline Cardoso Almeida-Brasil, Luana Faria Cruz, Lais Lessa Pantuzza, Mariana Guimarães Lima, Maria das Graças Braga Ceccato. *Department of Social Pharmacy, Faculdade de Farmácia - Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*

Background: The use of medicines aims to achieve better clinical outcomes. However, it may negatively influence one's perception of his/her quality of life (QoL). Most studies on drug utilization and QoL used specific population, as elderly or people with chronic diseases (CD), and there are few studies with the general population attended in primary health care (PHC).

Objectives: The aim was to evaluate the utilization pattern and the influence of medication use on quality of life among patients under care in public health centres (HC).

Methods: This is a cross-sectional study with patients aged over 18 years and under care at four public HC in Belo Horizonte, Brazil. Data were collected from September 2013 to April 2014 through interviews using a semi-structured questionnaire to get information about sociodemographics, drug utilization, lifestyle, self-perceived state of health and QoL. Drug utilization was the dependent variable, investigated by the question 'Have you used any medicines in the last 15 days? Which ones?' QoL was assessed using WHOQOL-BREF instrument. The drug utilization pattern was evaluated using chi-square test. We also used Pearson correlation to assess if the number of drugs affected the QoL scores. The difference in QoL between pharmacological classes was investigated using test t and ANOVA. Statistical significance was set at 5%.

Results: We included 930 (79.9% females) adults. Medicine use prevalence was 77% with a mean of 2.44 drugs. The most commonly used medications were those for the cardiovascular (37.9%) and nervous systems (29.6%). Higher age, lower education, unemployment, presence of two or more CD and worse self-reported health were related with drug utilization ($p < 0.001$). The use of any medicine was associated with worse QoL, and an increase in the number of medications used were related with a decrease in QoL scores ($p < 0.01$). The use of antidepressants and antacids worsened patients' QoL ($p < 0.01$).

Conclusions: The use of medicines showed a negative influence on the individual's perception of their QoL. The results are important to provide information to public policies in PHC, such as practices that promote the rational use of medicines.

289. Health literacy skills and correct use of medicines in the Netherlands: a study in community pharmacies

Ellen S Koster, Daphne Philbert, Marcel L Bouvy. *UPPER, Pharmacoepidemiology and Clinical*

Pharmacology, Utrecht University, Utrecht, The Netherlands

Background: Health literacy is defined as the ability to obtain, understand and apply information to make appropriate health decisions. Health literacy is specific and depends on the context, meaning that each situation requires specific skills. Most previous research has been performed in the US, and research in the context of medication use is limited.

Objectives: The study aimed to study the prevalence of limited health literacy among adult pharmacy visitors in the Netherlands and to assess the association between health literacy and understanding of medical information.

Methods: A cross-sectional study was performed in 33 community pharmacies belonging to the Utrecht Pharmacy Practice network for Education and Research. Adult pharmacy visitors (aged ≥18 years) were approached in the pharmacy waiting area and invited for a brief interview including the Newest Vital Sign (NVS), a validated health literacy assessment measure, and questions about understanding of standard drug label instructions.

Results: A total of 984 pharmacy visitors were included in the study (44% response rate): 63% were female, mean age was 56 years and the majority was of native origin (84%). Based on NVS scores, 52% had limited health literacy skills. Pharmacy visitors with limited health literacy skills had significant lower understanding of drug label instructions ($p < 0.001$).

Conclusions: Approximately half of the pharmacy visitors in this study had limited health literacy skills. These individuals experienced more difficulties understanding medical information. There is a need to identify patients with limited literacy skills in an early stage of treatment to provide tailored care as these patients might be at increased risk for drug-related problems caused by misunderstanding of information.

290. An educational intervention to improve the knowledge and practice of pharmacovigilance among healthcare professionals in private hospitals in Lagos state, Nigeria

Chioma S Ejekam,[1,2] Vivian O Chuka-Ebene,[1,3] Ibrahim A Oreagba,[1,3] SO Olayemi,[3] AJ Adewumi.[1,4]

[1]SouthWest Zonal Pharmacovigilance Centre, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria [2]Department of Community Health, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria [3]Department of Pharmacology, Therapeutics and Toxicology, College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria [4]Accident and Emergency, Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria

Background: The current thrust of pharmacovigilance (PVG) in Nigeria is creating awareness of the need to detect and report adverse drug reactions (ADRs) through spontaneous reporting. Spontaneous reporting of ADRs has faced the challenge of underreporting, and studies have suggested educational intervention as a way to improve reporting. The private sector is the first point of contact for most Nigerians seeking health care considering their number and closeness to the community. Appropriate practice of PVG will require total involvement of the private medical practitioners.

Objectives: The study aimed to assess the effect of an educational intervention on the knowledge and practice of PVG among healthcare professionals in private hospitals in Lagos state.

Methods: This was a cross-sectional study followed by a prospective intervention with the use of a pretested 'pre-test'and 'post-test' self-administered questionnaire to 121 healthcare professionals (doctors, nurses and pharmacists) from 72 selected private hospitals in Lagos state.The pre-test questionnaire assessed baseline knowledge, attitude and practice of PVG. A 5-h training was conducted; then a post-test intervention knowledge was assessed. Reminders for ADR reporting were sent via emails and SMS to respondents. This report presents a 1-month monitoring of the level and quality of ADR reporting. A paired *T*-test was used to compare the mean knowledge scores. Data were analysed using SPSS version 17.

Results: Pre-intervention knowledge and practice were unsatisfactory, but at the end of the training, the mean knowledge significantly improved from 6.59 ± 2.84 to 9.65 ± 2.04 ($p = 0.0000$). This improvement in the knowledge of PVG did not reflect in the level of reporting as one ADR report was received within the 1-month period; however, the quality was good; required fields were properly filled.

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Conclusions: Knowledge of PVG can be improved through regular educational intervention, but other effective means might be needed to improve levels of reporting of ADRs. This study is still ongoing, 3- and 6-month follow-ups and assessment are anticipated.

291. Clinical manifestations and treatment patterns of systemic lupus erythematosus

Sreedharan Nair, Sowmya Annavarapu, Vijayanarayana Kunhikatta, Girish Thunga. *Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal, India Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal, Karnataka, India*

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with clinical manifestation varying geographically. The treatment pattern of SLE is highly individualized depending on the clinical features.

Objectives: The study aimed to understand the clinical manifestations, treatment and outcome of SLE in a tertiary care teaching hospital.

Methods: Retrospective observational study conducted in a tertiary care teaching hospital after obtaining Institutional Ethics Committee approval. Demography, clinical manifestations, treatment and outcome of SLE patients admitted during 2010 to 2012 were collected. Treatment outcomes were assessed using SLEDAI and ECLAM scoring indexes, comparing baseline score and score at the last admission. Wilcoxon signed-rank test was used to compare disease activity indexes during first and last admission.

Results: A total of 93 patients were included. Average age at onset was 29.3 ± 8.5 years with female to male ratio of 15:1.9. The most common clinical manifestation was arthritis (74.3%), fever (71.4%) and malar rash (52.9%). Combination of prednisolone, hydroxychloroquine and cyclophosphamide was used in 44.1% of patients. SLEDAI and ECLAM disease activity indexes showed statistically significant improvement in patients treated with above combination.

Conclusions: Clinical manifestations of SLE were similar to studies conducted in other regions of India, and manifestations were effectively managed by combination of prednisolone, hydroxychloroquine and cyclophosphamide in our study population.

292. Prevalence and predictors of medication non-adherence in patients with mental disorders: a cross-sectional study

Gurumurthy Parthasarathi,[1] Jisha Jojo,[1] Madhan Ramesh,[1] Krishna Undela,[1] Dushad Ram.[2] *[1]Pharmacy Practice, JSS College of Pharmacy, JSS University, Mysuru, Karnataka, India [2]Psychiatry, JSS Medical College and Hospital, JSS University, Mysore, Karnataka, India*

Background: Medication adherence is important in the treatment of mental disorders to achieve the desired treatment outcomes.

Objectives: The study aimed to determine the prevalence and predictors of medication non-adherence amongst patients with mental disorders.

Methods: A cross-sectional study was conducted over a 2-year period in the outpatient psychiatric department of a south Indian tertiary care teaching hospital. All patients aged ≥18 years, diagnosed with mental disorders and receiving one or more psychotropic medication(s) for a period of at least 1 month were included in the study. Medication adherence was assessed using the Medication Adherence Rating Scale. Multivariate logistic regression analysis was applied to identify the predictors of medication non-adherence.

Results: A total of 1004 patients were included in the study. Median (IQR) age of the study population was 36 years (28–45 years). Male to female ratio was 1:1. About 18% of patients presented with comorbidities, and 11% were on polypharmacy (≥5 medications). Three-hundred eight-five (38%) patients were non-adherent to their medications. Patients' personal obligations (16.88%), ADRs (12.7%), cost of medications (7.7%) and lack of family support (7.01%) were the most common reasons for medication non-adherence. with comorbidities were two times more at risk to be non-adherent than their counterparts (RR 2.97, 95%CI [2.10, 4.22]; $p < 0.001$). Patients needing assistance to take medications were at higher risk to be non-adherent (RR 1.91, 95%CI [1.25, 2.91]; $p = 0.003$). In addition, those in the 18–59-year age group were also at higher risk for non-adherence (RR 2.65, 95%CI [1.45, 4.83]; $p = 0.001$). Patients receiving polypharmacy were at six times higher risk to be non-adherent than patients receiving <5 medications (RR 6.90, 95%CI [4.21, 11.32]; $p < 0.001$). Lower academic education was another predictor for non-adherence.

Conclusions: The leading predictor of non-adherence amongst Indian patients with mental disorders in this study was polypharmacy and may be due to an increased risk of ADRs and economic burden. Regular medication reviews may help to unnecessary medication use, improve adherence, reduce ADRs and achieve desirable outcomes.

293. Baseline antidiabetic drug patterns in patients initiating treatment for diabetes

Donnie P Funch,[1] Li Zhou,[1] Atheline Major-Pedersen,[2] Helge Gydesen,[3] David D Dore.[1] *[1]Epidemiology, Optum, Life Sciences, Waltham, MA, USA [2]Global Safety, Novo Nordisk A/S, Søborg, Denmark; [3]Epidemiology, Novo Nordisk A/S, Søborg, Denmark.*

Background: Studies of antidiabetic drugs (AD) are complicated by patients' prior AD use. Efforts to characterize baseline drug use have included counts of AD in baseline and type of baseline drug.

Objectives: The study aimed to identify specific measures of baseline use that improve control of confounding.

Methods: Using a U.S. claims database from 2010 to 2013, we evaluated baseline (6 months) patterns of AD use in >330 000 adult (≥18 years) initiators of five categories of AD. Initiation categories included metformin, sulfonylureas (SU), dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone, and glucagon-like peptide-1 receptor agonists (GLP-1 RAs; exenatide and liraglutide separately).

Results: Overall, 61.4% of initiators had no baseline use of ADs, while 6.2% initiated a second drug. Metformin initiators were most likely to have no baseline use of another AD (83.6%) and GLP-1 RA initiators least likely (26.6%). Among those with baseline AD use, metformin was the most frequent single AD dispensed (55.4%) followed by SU (30.9%) and insulin (26.7%). Only 10.2% of initiators had two ADs in baseline, most commonly metformin with SU (32.4%) or insulin (17.0%). Baseline use of ≥2 drugs was highest for exenatide (35.6%) and liraglutide initiators (39.3%). Baseline use of GLP-1 RAs ranged from 1.0% for metformin to 3.1% for TZD initiators, while use of other drugs varied considerably (insulin use ranged from 6.8% for metformin to 28.0% for liraglutide initiators). Among the top drug patterns, 55.3% received an AD in the month preceding initiation, and 36.9% appeared to use an AD regularly across the 6 baseline months. Patients on multiple drugs tended to have similar use patterns for those drugs across the 6 months.

Conclusions: Variation in AD use patterns across time and across incident drug categories may reflect distinct patient attributes, and accounting for these patterns may improve confounding control.

294. Multiple imputation (MI) for missing outcome data in a medical chart review study

Xiaojuan Li,[1] Violeta Hennessey,[2] Fei Xue.[3] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, USA [2]Global Biostatistical Science, Amgen, Inc., Thousand Oaks, CA, USA [3]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, USA*

Background: Missing outcome data due to incomplete medical chart retrieval are a common problem in studies when outcome is confirmed through chart review, resulting in missing information and potential bias. MI is a useful method to handle missing data. It is unclear, however, how MI based on internal validation data performs in this situation.

Objectives: The study aimed to evaluate the performance of MI based on internal validation results to handle missing outcome data in a study of osteonecrosis of the jaw (ONJ).

Methods: Cases of potential ONJ (PONJ) were identified from women ≥55 years with post-menopausal osteoporosis who initiated a bisphosphonate (BP) using relevant ICD-9 codes in the MarketScan database (2004–2012). Their true case status (D) was determined using an alloyed gold standard based on frequency and interval of diagnosis and treatment. We randomly sampled 30% of all PONJ cases to use as a hypothetical validation subgroup and assumed that D was available only for this group. We built a prediction model for D using selected covariates in this group and obtained a predictive distribution of covariate coefficients, which was applied to impute D (D') in the rest of the 70% sample using MI. We estimated the positive predictive value (PPV) with 95%CI and compared it to that of analysis in (1) the full cohort of all PONJ cases and (2) the validation subgroup. Sensitivity (SE) and specificity (SP) of the MI approach in the 70% sample were calculated by comparing D' to D.

Results: Out of the 440 825 BP users, 363 had PONJ events, and 35 were confirmed. Random sampling

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yielded a validation subgroup of 110 PONJ cases (and 10 true cases). In the full cohort with D, the estimated PPV was 9.6% (6.6–12.7%). Restricting the analysis to the validation subgroup yielded a PPV of 9.1% (3.7–14.5%). The MI approach with 40 repetitions produced a PPV of 9.5% (4.5–14.5%). The SE and SP of this approach were 0.17 and 0.91, respectively, and increased slightly as the size of the validation subgroup increased.

Conclusions: MI can be used to derive missing case data and inform aggregative data analysis when internal validation results are available. However, it is not advisable to use MI to derive individual-level case status.

295. Applying the ready reckoner (RRec) tool for assessing antipsychotic (AP) prescribing within post-authorisation safety studies (PASS)

Deborah Layton. *Drug Safety Research Unit, Southampton, Hampshire, UK*

Background: In the UK, the RRec monitors AP dosing in patients (pts) with complex AP regimens; each AP dose is converted to % of relevant max dose by indication and titration stage in SPC. Total dose % >100% identifies pts at risk. A nested case control (NCC) study was undertaken as part of a PASS to explore possible dose-event response for somnolence/sedation (SS) after starting a new AP formulation. The primary objective evaluated total daily dose (TDDmg) >600.

Objectives: An exploratory objective evaluated the use of the RRec as an alternative indication-adjusted dose metric to model AP treatment effects.

Methods: An incidence density matched NCC study using a primary care cohort (13 276) identified September 2008 to February 2013. Of the 756 cases, 212 (28%) were randomly selected and 170 risk sets created. For all subjects, the reported TDDmg (start, maintenance, and event) were converted to dose % (non-licenced indications used SPC dose range for major depression). Fractional polynomial (FP) logistic models explored functional form; empirical and fitted within-person OLS dose trajectories described patterns over time.

Results: SS cases tended have higher reported TDDmg vs controls at start [median 300 (IQR 200,600) vs 200 mg (IQR 100,300), $p < 0.01$], but the inverse was seen when the dose % metric was applied (median 50% (IQR 16 100) vs 75% (33 100), $p = 0.02$). At maintenance and event, similar relationships were observed for reported TDDmg and dose % variables. SS risk was a negative function of TDDmg and dose %. No deviation from linear assumption was apparent for start and maintenance doses (FP2 vs linear, $p > 0.05$) but was nonlinear for dose % at event ($p = 0.04$). In exploring pattern over time, the general trend was decreasing for both cases and controls, although slower for controls.

Conclusions: This exploratory analysis demonstrates the feasibility of the RRec as an alternative indication-adjusted variable for analysing dose, particularly where multiple indications may exist that use various dose ranges. Analytical advantages include avoiding creation of strata of small sample sizes. Limitations include possible metric underestimation from missing data for other concomitant APs.

296. Drug utilization study (DUS) methodology: applications and challenges

Dara Stein, Kristin A Hanson. *Value Demonstration, UBC: An Express Scripts Company, Dorval, QC, Canada*

Background: Increasingly, real-world observational DUS are being conducted as part of the marketing authorization process or post-market approval to assess risk management activities, off-label drug use, safety and effectiveness.

Objectives: The study aimed to determine the best approach for conducting observational DUS in Europe, North America and select ROW countries.

Methods: Lessons learned from experience with designing and implementing DUS have been delineated. Scientific and operational methodological considerations have been evaluated and summarized.

Results: Three of the 12 studies were mandated by the EMA or FDA. Sample sizes ranged from 125 to 2000 patients; number of study centers ranged from 1 to 300. Therapeutic areas included oncology, cardiology, intensive care, CNS disorders, renal, infectious and rare diseases. Five studies were conducted retrospectively by secondary data collection from patient medical charts, and seven studies were conducted prospectively. Common design considerations included identifying optimal eligibility/enrollment and study/follow-up periods for data

collection. For studies assessing off-label use, a retrospective chart review design should be considered to mitigate the Hawthorne effect wherein physicians change their behavior based on awareness of being observed. The creation of a detailed site recruitment plan can help mitigate operational challenges in site recruitment, especially if the study will be conducted in consecutive waves over time. Understanding the commercial availability of the sponsor product at study initiation is essential to determine whether there is any impact on design classification and ethics/regulatory requirements in countries included in the study.

Conclusions: While observational DUS can provide valuable insight into prescription patterns (e.g., off-label drug use) in usual care settings, they are not without limitations. It is imperative to determine the most appropriate study design (i.e., retrospective vs. prospective) to achieve study objectives. Once the appropriate design is chosen, methodological and operational challenges can be mitigated if identified and addressed at study outset.

297. Automated extraction of VTE events from narrative radiology reports in electronic health records: a validation study

Zhe Tian,[1,2] Simon Sun,[3] Tewodros Eguale,[2,4] Christian Rochefort.[1,2,5] *[1]Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada [2]Clinical and Health Informatics Research Group, McGill University, Montreal, QC, Canada [3]Radiology, McGill University, Montreal, QC, Canada [4]Brigam Women's Hospital, Boston, MA, USA [5]Ingram School of Nursing, McGill University, Montreal, QC, Canada*

Background: Close surveillance of venous thromboembolism (VTE) is a key step to determine the effective use of thromboprophylaxis. Using manual chart review and discharge diagnostic may take up to few months before adequate information is available, thus making any inefficient use of thromboprophylaxis hard to intervene. With the dissemination of electronic health record, symbolic natural language (NLP) processing emerged as a potential solution to these issues.

Objectives: We assessed the accuracy of using symbolic NLP to identify the two clinical manifestations of VTE, deep vein thrombosis (DVT) and pulmonary embolism (PE), from narrative radiology reports.

Methods: A random sample of 4000 narrative reports was selected among imaging studies that could diagnose DVT or PE and that were performed between 2008 and 2012 in a university health network of five adult-care hospitals in Montreal (Canada). The reports were coded by clinical experts to identify positive and negative cases of DVT and PE, which served as the reference standard. Using data from the largest hospital ($n = 2788$), two symbolic NLP classifiers were trained, one for DVT, the other for PE. The accuracy of these classifiers was tested on data from the other four hospitals ($n = 1212$).

Results: On manual review, 663 DVT-positive and 272 PE-positive reports were identified. In the testing dataset, the DVT classifier achieved 94% sensitivity (95%CI [88%, 97%]), 96% specificity (95%CI [94%, 97%]) and 73% PPV (95%CI [65%, 80%]), while the PE classifier achieved 94% sensitivity (95%CI [89%, 97%]), 96% specificity (95%CI [95%, 97%]) and 80% PPV (95%CI [73%, 85%]).

Conclusions: Symbolic NLP can accurately identify VTEs from narrative radiology reports. This method could facilitate VTE surveillance and the evaluation of preventive measures.

298. Physicians' acceptance of pharmacists' interventions in a Dutch university hospital

Rianne J Zaal,[1] Edwin W den Haak,[2] Arnold G Vulto,[1] Patricia MLA van den Bemt.[1] *[1]Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands [2]Utrecht University, Utrecht, The Netherlands*

Background: Knowledge on physicians' acceptance of pharmacists' interventions and determinants for acceptance, which is important to optimize central pharmacy services, is limited.

Objectives: The study aimed to determine the physicians' acceptance rate of pharmacists' interventions and to identify determinants for acceptance.

Methods: A retrospective case-control study was performed in adult patients admitted to a university hospital in the Netherlands. Pharmacists' interventions regarding drug–drug interactions and drug dosing in patients with renal failure that were recorded in the electronic medical record from January 2012 until June 2013 were

extracted. The primary outcome was the proportion of accepted interventions, which was assessed by reviewing the computerized physician order entry system and electronic medical records. Univariate and multivariate logistic regression analysis was performed to identify determinants for physicians' acceptance as secondary outcome. Characteristics of the intervention, patient, pharmacist and physician were included in the analysis as potential determinants for acceptance.

Results: A total of 842 interventions relating to 607 patients were included. Most frequently proposed interventions concerned drug–drug interactions (46.3%) and supratherapeutic dosages (21.9%). Six-hundred interventions (71.3%) were accepted, and 191 (22.7%) were not accepted; acceptance could not be assessed for 51 (6.1%) interventions. After multivariate logistic regression analysis, the number of medication orders (ORadj 1.07; 95%CI [1.03, 1.10]), continuation of pre-admission treatment (ORadj 0.62; 95%CI [0.45, 0.86]) and pharmacotherapeutic group of the drug (antineoplastics and immunomodulators ORadj 0.41; 95%CI [0.17, 0.98]) were significantly associated with acceptance.

Conclusions: The majority of pharmacists' interventions are accepted by physicians, and the probability for acceptance increases for patients with an increasing number of medication orders. Interventions regarding continued pre-admission treatment or antineoplastics and immunomodulators are less likely to be accepted. To optimize central pharmacy services, further insight into physicians' reasons for non-acceptance is necessary.

299. Mind the gap: why closing the doughnut hole is insufficient for Medicare specialty drug users

Stacie B Dusetzina,[1,2] Nancy L Keating.[3] *[1]Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [2]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [3]Health Care Policy, Harvard Medical School, Boston, MA, USA*

Background: Specialty pharmaceuticals are the fastest growing class of prescription drugs. The Affordable Care Act will close the Part-D coverage gap by 2020, decreasing out-of-pocket (OOP) costs for many patients. How much these changes will reduce OOP costs for specialty drug users is unknown.

Objectives: We estimated annual OOP prescription drug costs for enrollees prescribed oral oncologics across all Medicare Part D plans in 2015, after the doughnut hole closes in 2020.

Methods: Using formulary data from CMS for 1114 stand-alone and 2230 Medicare Advantage Part-D plans, we estimated the 2015 annual OOP costs for each of five selected oral oncologics (imatinib, nilotinib, erlotinib, sunitinib AND enzalutamide), assuming chronic use for a year. We obtained the average monthly cost for each drug from the CMS Formulary data for plans covering the selected product. We calculated annual OOP costs by first calculating the deductible plus the coinsurance/copayments for the initial coverage period up to $2960. We next calculated the OOP costs in the coverage gap (45% in 2015) up to $4700 (OOP limit). Finally, we calculated the costs in the catastrophic period through the end of the benefit year. We repeated calculations for 2020, after the donut hole is closed, with which the only change was the reduction of cost sharing in the coverage gap to 25%.

Results: Mean and median annual OOP costs for individuals taking oral oncologics were similar for patients in stand-alone Part-D plans and Medicare Advantage Part-D plans. Median (interquartile range) OOP costs for patients in stand-alone plans ranged from $5349 ($5341–5364) for enzalutamide to $11 932 ($11 876–12,036) for sunitinib. In 2020, median annual OOP costs for the same drugs ranged from $5019 ($5012–5,033) and $11 603 ($11 554–11 705), respectively, representing OOP cost savings of approximately $330 per year.

Conclusions: Closing the doughnut hole does little to reduce patient OOP spending on specialty drugs. The similarity in coverage design suggests that patients may be unable to find a plan that will further reduce their cost-sharing.

300. Treatment patterns and outcomes of patients diagnosed with ovarian cancer in the Netherlands: a registry study

Eline Houben,[1] Heleen GM van Haalen,[2] Wouter Sparreboom,[1] Jetty A Overbeek,[1] Nicole Ezendam,[3] Hannie JMA Pijnenborg,[4] Myrthe PP van Herk-Sukel.[1] *[1]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands [2]AstraZeneca, Zoetermeer, The Netherlands [3]Comprehensive Cancer*

Centre the Netherlands, Eindhoven, The Netherlands [4]Tweesteden Ziekenhuis, Tilburg, The Netherlands

Background: Little information is available on the patterns of chemotherapy for the treatment of ovarian cancer (OC) and the resulting survival outcomes.

Objectives: The study aimed to describe the current chemotherapy patterns for OC and to evaluate survival outcomes following subsequent lines of chemotherapy.

Methods: Data from Eindhoven Cancer Registry (ECR), including data on all newly diagnosed cancer patients, were linked to the PHARMO Database Network (PHARMO) including, among other things, information on inpatient and outpatient drug use. Patients diagnosed with primary OC between 2000 and 2010 were selected. First and subsequent chemotherapy regimens were defined as the start of a different (combination of) chemotherapeutic agent(s) or a gap >42 days between two treatment cycles. Median survival after first- and second-line chemotherapy was determined and stratified by type of chemotherapy.

Results: From the ECR-PHARMO cohort, 261 OC patients with detailed chemotherapy data available were selected. Of those, 95% received chemotherapy as initial treatment. Pathological tumor stage was recorded for 77% of patients, of whom 11%, 55%, and 17% of patients had disease stage II, III, and IV, respectively. In first-line chemotherapy, 76% of patients received platinum/taxane doublet chemotherapy. Of the 161 patients receiving second-line chemotherapy, platinum-containing chemotherapy was received by 63% of patients (101 of whom 13 (13%) received platinum monotherapy). In third-line chemotherapy, this was 51% (53 patients). At least eight lines of chemotherapy were identified in 12 cases. Median survival after first-line chemotherapy was 32 months, and after second-line chemotherapy, this remained 14 months. Patients treated with platinum-based chemotherapy showed median survival of 34 months compared with 10 months for patients treated with non-platinum-based chemotherapy in first-line chemotherapy. For second-line chemotherapy, this was 23 and 11 months, respectively.

Conclusions: This study provides detailed information on the type of chemotherapy regimens administered to OC patients at initial diagnosis and during subsequent lines of chemotherapy as well as the survival following these lines of chemotherapy.

301. Predictors of gastrointestinal bleeding among patients with atrial fibrillation initiating dabigatran and subsequent patterns of use

Julie C Lauffenburger,[1] Denise H Rhoney,[2] Joel F Farley,[3] Anil K Gehi,[4] Gang Fang.[3] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [2]Division of Practice Advancement and Clinical Education, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [3]Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [4]Division of Cardiology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA*

Background: In patients with atrial fibrillation using dabigatran for stroke prevention, the risk of gastrointestinal (GI) bleeding has been shown to be potentially elevated compared with warfarin. Little is known about the risk factors associated with GI bleeding in patients using dabigatran in clinical practice or subsequent re-initiation patterns.

Objectives: The study aimed to examine patient demographic and clinical risk factors and their associations with GI bleeding in patients using dabigatran and re-initiation patterns after GI bleeding.

Methods: A cohort of non-valvular AF patients newly initiating dabigatran was extracted from a nationwide database of commercial and Medicare Part D supplement claims from 2010 to 2012. Patients were followed until switching, loss of eligibility, GI bleeding, or censoring. We used bivariate and multivariate Cox regression to estimate the effect of baseline demographic and clinical characteristics on the risk of a GI bleeding event in patients using dabigatran. Patterns of anticoagulation use after GI bleeding were also examined descriptively.

Results: In total, 21 033 patients initiated dabigatran, and 466 (2.1%) experienced GI bleeding during a follow-up. Male gender was associated with a lower risk (aHR: 0.78, 95%CI [0.64, 0.95]) of GI bleeding. Compared with those <55 years of age, age 55–64, 65–74, and ≥75 years yielded aHRs of 1.54 (95%CI [0.89, 2.68]), 2.72 [1.59, 4.65], and 4.52 [2.68, 7.64], respectively. Renal impairment (aHR: 1.67, 95%CI [1.24, 2.25]), heart failure

(aHR: 1.25, 95%CI [1.01, 1.56]), alcohol abuse (aHR: 2.57, 95%CI [1.52, 4.35]), *H. pylori* infection (aHR: 4.75, 95%CI [1.93, 11.68]), antiplatelet therapy (aHR: 1.49, 95%CI [1.19, 1.88]), and digoxin use (aHR: 1.49, 95%CI [1.19, 1.88]) were also associated with an increased risk of GI bleeding. After GI bleeding, 193 patients (43.3%) reinitiated any anticoagulant, with a mean time of 50.4 days.

Conclusions: The risk of GI bleeding in patients using dabigatran is associated with increased age, comorbidities, and renal impairment, even after adjusting for other risk factors. Fewer than 50% of patients reinitiated an anticoagulant after a GI bleeding event.

302. Monitoring of mortality associated to new oral anticoagulants vs warfarin in atrial fibrillation

Flavia Mayer, Ursula Kirchmayer, Nera Agabiti, Giovanna Cappai, Danilo Fusco, Marina Davoli. *Department of Epidemiology, Lazio Regional Health Service, Rome, Lazio, Italy*

Background: New oral anticoagulants (NOA) were authorized for treatment of atrial fibrillation (AF) in Italy in July 2013. Evidence on related risks is controversial. The Lazio regional health authority commissioned a pilot real-time monitoring of all resident AF patients prescribed with NOA compared with warfarin.

Objectives: The study aimed to estimate the association between treatment with different oral anticoagulant drugs and occurrence of mortality in a pilot real-time monitoring based on health information systems.

Methods: We conducted a prospective cohort study to compare NOA with warfarin use. We identified new users of study drugs with hospital admissions or emergency room visits for AF in the 30 days before index prescription.

Monitoring was performed considering the first 6 months after authorization of NOAs for AF in Italy in July 2013 and adding consequently 3-month periods until June 2014, the latest updated of health information systems.

Follow-up started the day after index prescription and finished at occurrence of any event among death, regional health care disenrollment, switching to other anticoagulant and treatment discontinuation. We calculated crude rates and incident rate ratios (IRRs) of mortality in the cohort of NOA users respect to Warfarin users for the three monitoring periods of 6, 9 and 12 months, respectively.

Results: During the 12-month period, Warfarin use steadily decreased from 263 new users in July 2013 to 164 new users in June 2014, whereas NOA use increased from 11 to 152 new users.

Overall, 304 person-years were cumulated among warfarin users with 58 deaths, and we observed 31 deaths among NOA users in 317 person-years. Mortality IRRs in the three monitoring periods were 0.22, 0.58 and 0.51 respectively.

Conclusions: The first 12 months of anticoagulant monitoring showed an increasing use of NOA for AF patients. Concerns regarding increased mortality in NOA user were not confirmed.

Further analysis presented at ICPE will account for covariates within multivariate models and include additional outcomes such as cardiovascular mortality, incidence of major ischemic and haemorrhagic events. Moreover, the monitoring period will be extended.

303. The risk of urinary tract infections with the use of dextromethorphan in different indications. Results from a systematic review and meta-analysis of randomised clinical trials

Luis G Velez-Nandayapa,[1,2,3] Laura M DeVore.[1] *[1]Pharmacovigilance, Drug Safety Research Unit, Southampton, UK [2]Epidemiology, London School of Hygiene and Tropical Medicine, London, UK [3]Pharmacovigilance, Dr. Reddys's Laboratories, Basel, Switzerland*

Background: Dextromethorphan (DMP), an antitussive agent, is a common active ingredient in many OTC medicines. DMP has been studied, in randomised clinical trials, for many other indications, such as amyotrophic lateral sclerosis, reduction of pain, sedation, detoxification of alcoholism, opioid withdrawal, and treatment of pseudobulbar affect.

Objectives: We aimed, through a systematic review and meta-analysis (SR&MA), to provide a reliable assessment of the unintended effects of the use of DMP in different indications.

Methods: This SR&MA was registered with the PROSPERO database (CRD42015016631) as a protocol for an evaluation of the safety profile of DMP in the central nervous system (CNS).The search strategy

included randomised clinical trials using DMP in different indications, which were published from January 1990 to December 2014 in Medline, EMBASE and Cochrane Library databases. This SR&MA was conducted following the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses). The outcomes of interest evaluated were the number and type of adverse events reported. Analysis of odds ratio (OR), as a measure of effect, and 95% confidence intervals (CI95%) and *p*-values, as generated from the chi-squared, was calculated; heterogeneity was assessed using the I^2 test. Sub-analysis by doses (<120 vs ≥120 mg/day) was performed.

Results: Sixty-five publications were included for pooling of data, involving 6186 subjects. We found that evidence of associations, mainly in the CNS, was in accordance with published data. However, evidence of an unexpected association was found for urinary tract infections (UTIs) and the use of DMP vs control with OR 5.32; CI95% [1.58, 27.99]; $p=0.0025$; $I^2=72.8\%$ (events were 20/3447 vs 3/2739). A sub-analysis by dose (≥120 mg/day) showed OR 8.11; CI95% [1.07, 361.16]; $p=0.0195$; $I^2=0.00\%$ (events were 8/291 vs 0/287).

Conclusions: Our results suggest evidence of association between DMP and UTIs; however, the possibility of type I statistical error is present. Further studies are needed to confirm our findings.

304. Ocular beta-blockers in people with asthma and glaucoma

Daniel R Morales,[1] Brian J Lipworth,[2] Cathy Jackson,[3] Bruce Guthrie.[1] *[1]Medical Research Institute, University of Dundee, Dundee, UK [2]Scottish Centre for Respiratory Research, University of Dundee, Dundee, UK [3]School of Medicine, University of Central Lancashire, Dundee, UK*

Background: Beta-blockers cause exacerbations in susceptible people with asthma. Risk varies according to drug selectivity and dose of administration and may be greatest following acute exposure. Risk has been quantified for oral but not ocular beta-blocker exposure commonly used for glaucoma.

Objectives: The aim of the study was to measure ocular beta-blocker prescribing trends in people with asthma and glaucoma in UK primary care and the association between ocular exposure and asthma exacerbations.

Methods: Data from the UK Clinical Practice Research Datalink were used to form a cohort of people with active asthma in which the quarterly prevalence of ocular beta-blocker prescribing was measured from 2000 to 2012. Active asthma was defined by the presence of Read codes and the use of asthma medication. A nested case control study (NCCS) using four controls matched on age, gender and calendar time using incidence density sampling was used to calculate incidence rate ratios (IRR) for the association between ocular beta-blocker exposure and asthma hospitalisation or primary care asthma exacerbations (PCAE) defined by prescriptions for oral corticosteroids, using conditional logistic regression.

Results: The cohort included 4865 people with asthma and glaucoma experiencing 128 asthma hospitalisations and 598 PCAE during a follow-up. The prevalence of ocular beta-blocker prescribing at the end of the study period was 14.3%. The relative incidence of PCAE increased within 30 days of incident non-selective ocular beta-blocker exposure (IRR 4.52 (95%CI [1.45, 14.04])). The relative incidence of asthma exacerbations was not significantly elevated with prevalent exposure (IRR 1.11 (95%CI [0.80, 1.53])). Risk from incident selective ocular beta-blocker exposure could not be estimated due to few patients being exposed.

Conclusions: Non-selective ocular beta-blockers are commonly prescribed to people with asthma and glaucoma, and new exposure appears to carry a short-term risk of asthma exacerbation in susceptible people. It remains unclear whether new use of selective ocular beta-blockers has any clinically significant adverse respiratory effects.

305. Can reporters of a medicine incident accurately reflect the clinical risk?

Alice V Gilbert,[1,2] Michael Roberts,[2,3] Des Williams,[3] Andrew L Gilbert.[3] *[1]Pharmacy, Top End Health Service, Darwin, Northern Territory, Australia; [2]School of Medicine, University of Queensland, Brisbane, Queensland, Australia; [3]Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia*

Background: Medication incidents are the second highest reported category of incident within healthcare in Australia. Incident reporting is a requirement within our public hospitals, but little is known

about the accuracy of incident severity rating by incident-reporters.

Objectives: To compare Incident Severity Rating (ISR) scores entered by the incident-reporters and a panel of health professionals.

Methods: The ISR was developed after analysis of methods used nationally and internationally. The ISR uses a 5 point Likert scale for measuring the impact caused to the person(s) affected by an incident. ISR 1 indicates the most severe event (including sentinel events), and ISR 5 the lowest. A retrospective audit of a random sample of medication incidents reported in an Australian Australian tertiary hospital, over a 3 year period, were reviewed independently by a panel of health professionals to assign an ISR. The review panel consisted of a doctor, a clinical pharmacist and a registered nurse. A Kappa score was used to determine the inter-rater agreement. The initial reporters ISR's were compared to that of the review panel. A Kappa score was then used to determine the accuracy of the initial rating.

Results: 458 medicine incident reports were entered over 3 year time period (2010 to 2013). A random sample of 90 (20%) reports was selected for analysis; 6 reports were excluded as they were duplicates of the same incident. The review panel demonstrated a Po 0.78 overall agreement between themselves. When original reporters ISR were included, the Kappa agreement dropped to Po 0.56. The review panel gave identical ratings for 57 incidents (68%) with the initial reporter entering the same ISR for 21 for the 57 (37%) incidents. 10 incidents (12%) were rated-ISR 1 or 2 by the review panel. Original reporters identified 1 ISR 1 and 4 ISR's 2. The multidisciplinary panel each would have raised the severity of 1 of the 4 incidents (that the original reporter rated as ISR 2) and would have classified it as an ISR 1 and downgraded the remaining 3 ISR 2's to ISR 3-5.

Conclusions: This study indicates that there is potential for incidents that require a full review being overlooked by organisations due to the initial ISR given by the reporter. A clinical panel has the ability to more correctly assign risk ratings, which could enable further review and, if necessary, quality improvement activities to reduce the occurrence of similar medication incidents and target trends.

306. Pharmacovigilance practices for better healthcare services: knowledge, awareness, and practices of healthcare professionals (HCPs) towards pharmacovigilance in Malaysia

Muhammad Shahid Iqbal,[1] Mohd Baidi Bahari,[1] Muhammad Zahid Iqbal,[1] Muhammad Waseem Iqbal.[2] [1]*Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, AIMST University, Semeling, Kedah Darul Aman, Malaysia* [2]*Faculty of Law, University of Malaya, Kualalumpur, Wilayah Persekutuan, Malaysia*

Background: Pharmacovigilance knowledge and awareness play a major role in improving patient health status by monitoring the post-marketing safety of medicines. In Malaysia, no study has been done on the knowledge and awareness of healthcare professionals (HCPs) towards pharmacovigilance concept.

Objectives: The aim was to investigate the knowledge, awareness, and practices of the HCPs towards pharmacovigilance concept in Malaysia.

Methods: A cross-sectional self-administered study has been conducted at tertiary level hospital in Malaysia. The research questionnaire comprised various questions assessing the knowledge, awareness, and practices of HCPs towards pharmacovigilance. Face and content validity of the research tool was done by various HCPs including academics, consultants, pharmacists, and senior nurses. All statistical analyses were done using SPSS version 21.0.

Results: Around 218 HCPs responded in the study with a response rate of 77%. Among HCPs, physicians 33%, pharmacists 64%, and nurses 41% participated. Interestingly, around 40% of the HCPs were not familiar with term pharmacovigilance and its benefits. Conversely, 89% of HCPs believe that reporting adverse drug reaction (ADR) is a responsibility of all type of HCPs and they consider it as one of their obligations to know pharmacovigilance. Furthermore, around 69% of the HCPs were aware of look-alike and sound alike medications, and around 70% considered it difficult to know if the event is ADR or not. However, almost 52% of the HCPs did not know exactly which regulatory body is responsible to handle ADR reports and other pharmacovigilance measures.

Conclusions: HCPs working at tertiary-level hospitals are not sufficiently aware of pharmacovigilance concept and its benefits. However, a positive behavior

towards the importance of the pharmacovigilance concept was observed. The concerned regulatory body should take initiatives to improve the knowledge and awareness about pharmacovigilance among HCPs.

307. Adverse drug reactions (ADRs) reporting among community health extension workers (CHEWs) in Oyo State, Nigeria: an assessment of attitude and practice

Waheed A Adedeji,[1,2] Fatai A Fehintola.[1,2] *[1]Clinical Pharmacology Department, University College Hospital, Ibadan, Oyo, Nigeria [2]Pharmacology and Therapeutics, University of Ibadan, Ibadan, Oyo, Nigeria*

Background: Adverse drug reactions (ADRs) remain a significant cause of iatrogenic disease worldwide, and it is associated with high morbidity, mortality and heavy economic loss. Spontaneous reporting has contributed immensely towards the prevention of serious ADRs, and there is a need to study the role of community health extension workers (CHEWs), which constitute the highest number of health workers in the primary health care in Nigeria.

Objectives: The study aimed to assess the attitude and practice of ADRs reporting among the community health extension workers (CHEWs) in Oyo State, Nigeria.

Methods: A cross-sectional survey of CHEWs in the employ of Oyo State, Nigeria, using self-administered questionnaires from 333 CHEWs randomly selected from the five administrative zones of the state.The questionnaire was used to assess the attitude and practice of CHEWs towards ADRs and factors influencing ADRs reporting. The attitude questions were scored and categorized into positive and negative attitude.

Results: Two hundred and forty-six respondents (73.9%) agreed that ADRs constituted an important problem in medical practice; however, only 192 (57.7%) always consider ADRs before dispensing or administering drugs. One hundred and eighty-four (55.3%) respondents have observed ADRs before, but only 11 (6%) have reported it with yellow forms. Two hundred and nine respondents (62.9%) had negative attitude towards ADRs reporting. There is significant relationship between ADRs reporting and attitude ($p < 0.001$). Other factors observed to influence ADRs reporting were inadequate exposure to formal instructions on pharmacovilance ($p = 0.012$), lack of time to adequately look for ADRs while at work ($p = 0.015$) and complexity of the yellow forms ($p < 0.001$).

Conclusions: The ADRs' reporting rate was low among the CHEWs in Oyo State, Nigeria. There is a need for an interventional programme towards improving ADRs reporting among the CHEWs.

308. New methodology for enhanced safety surveillance of nasal quadrivalent live attenuated influenza vaccine (QLAIV) using participant questionnaire feedback: interim results

Rhian McNaughton, Elizabeth Lynn, Vicki Osborne, Saad Shakir, Abigail Coughtrie. *Drug Safety Research Unit (DSRU), Bursledon Hall, Blundell Lane, Southampton, Hampshire, UK*

Background: An active surveillance study was performed at the start of the 2014/2015 influenza season following publication of EMA guidance for enhanced safety surveillance of influenza vaccines.

Objectives: The study aimed to rapidly detect a clinically significant change in the frequency and/or severity of expected 'reactogenicity' and other adverse events of interest (AEIs) during the first 14-day post-vaccination with intranasal QLAIV (Fluenz Tetra®).

Methods: Children and adolescents vaccinated with QLAIV were recruited to this prospective observational cohort study through GPs or schools in pilot areas in England during a mass influenza vaccination programme. Three age groups with 100 vaccinees in each were planned: Group 1: 2–4 years, Group 2: 5–10 years and Group 3: 11–17 years. Participants completed simple online or postal questionnaires detailing exposure, covariates (e.g. medical conditions) and targeted outcome information about AEIs (primary outcome). AEI summary descriptive statistics, crude incidence risks and incidence rates (IR) per 1000 patient-weeks (95%CI) were calculated.

Results: With data collected from September to November 2014, the cohort comprised 282 participants (Group 1: $n = 143$, Group 2: $n = 103$, Group 3: $n = 36$). The most frequently reported AEI was nasal congestion in all age groups (Group 1: $n = 67$ (46.9%), IR: 317.3 [244.2, 412.3]; Group 2: $n = 46$ (44.7%), IR: 264.6 [189.1, 370.3]; Group 3: $n = 15$ (41.7%), IR: 295.2 [174.8, 298.4]. Although four hypersensitivity type reactions

were reported (Group 1: $n=1$, Group 2: $n=2$, Group 3: $n=1$), on a follow-up, none was a true allergic reaction, serious or required hospitalisation.

Conclusions: No apparent safety signal was detected from the small amount of data collected. This study demonstrates that the methodology applied is well suited to rapidly monitor the incidence of AEIs with QLAIV, minimising any additional workload for healthcare professionals.

309. What explains the different rates of human papillomavirus vaccination among adolescent males and females in the United States?

Yoonyoung Choi,[1] Efe Eworuke,[1,2] Richard Segal.[1] *[1]Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA [2]Division of Epidemiology II, Office of Surveillance and Epidemiology, Office of Pharmacovigilance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA*

Background: Despite universal recommendation of the HPV vaccine in both men and women in the US, adolescent males are less likely to receive the vaccine.

Objectives: The study aimed to identify socio-demographic factors associated with receiving HPV vaccination in adolescents at the national level and compare them between males and females.

Methods: We included adolescents 13–17 years old with a documented vaccination record from a healthcare provider in the National Immunization Survey-Teen 2012 dataset. The primary outcome was whether an adolescent received at least one dose of HPV vaccine or not. A logistic regression model was constructed with 13 socio-demographic factors along with significant interaction pairs with gender.

Results: Subjects included 10 426 boys and 9320 girls for the analysis. About half of the female adolescents (54%) received at least one dose of HPV vaccine, while only 21% of males received a vaccination ($p<0.05$). Five significant factors differed between males and females (all $p<0.02$): "age 17 years" (males odds ratio [mOR] = 1.22 vs. females odds ratio [fOR] = 2.40), "Hispanic" (mOR = 2.03 vs. fOR = 1.18), "non-Hispanic Black" (mOR = 1.47 vs. fOR = 0.75), "receiving provider recommendation for HPV vaccination" (mOR = 8.39 vs. fOR = 3.41), and "1–3 provider visits in previous year" (1 visit: mOR = 1.89 vs. fOR = 1.09, and 2–3 visits: mOR = 2.13 vs. fOR = 1.08). Among variables not showing a significant interaction with gender, having had a meningococcal vaccination was most strongly associated with HPV vaccination (OR = 5.28, $p<0.01$). For parents, the most common reasons for being unlikely to vaccinate their children were "not recommended by a health care provider" for adolescent males (23.5%) and "unnecessary" for female adolescents (19.6%).

Conclusions: Even after strong recommendations to vaccinate adolescent boys, vaccination rates remain lower for males compared with females. We found a significant interaction between gender and several socio-demographic variables in predicting vaccination uptake. This suggests that identical strategy would not improve the likelihood of vaccination in male and female adolescents to the same extent.

310. Safety of a novel meningococcal group B vaccine used in response to two outbreaks in the US

Jonathan Duffy,[1] Peter Johnsen,[2] Mary Ferris,[3] Mary Miller,[3] Kevin Leighton,[2] Mark McGilvray,[3] Lucy McNamara,[1] Lucy Breakwell,[1] Yon Yu,[1] Tina Bhavsar,[1] Elizabeth Briere,[1] Manisha Patel.[1] *[1]Centers for Disease Control and Prevention, Atlanta, GA, USA [2]Princeton University, Princeton, NJ, USA [3]University of California Santa Barbara, Santa Barbara, CA, USA*

Background: *Neisseria meningitidis* serogroup B (MenB) infections can be fatal. A novel MenB vaccine (4CMenB) was used under an expanded access investigational new drug protocol in response to outbreaks at two universities.

Objectives: The study aimed to evaluate the safety of 4CMenB.

Methods: Two doses of 4CMenB were given >30 days apart to undergraduates, dormitory residents, and persons with high-risk medical conditions. Mass vaccination clinics were held December 2013 to May 2014. Adverse events (AEs) were identified by observation for 15 minutes following vaccination; spontaneous reporting by phone, email, or clinic visits; written surveys following each dose; and local hospital visit surveillance. Serious adverse events (SAEs) were defined as death, a life-threatening

event, hospitalization, persistent or significant incapacity, or birth defects. Causality was assessed for each SAE.

Results: A total of 28 229 doses were administered to 15 346 persons with a median age 20 years (range 16–65). Among dose 1 recipients, 94% returned for dose 2 at university A and 78% at university B. During the 15-min observation, the incidence of presyncope was 2/1000 doses, and syncope was 0.5/1000 doses. AEs were spontaneously reported by 4% of participants; the most common were arm pain and fever. There were 50 SAEs, including 8 cases of appendicitis (1.19/1000 person-years). Causal association with vaccine was suspected for two SAEs: anaphylaxis and rhabdomyolysis (both patients recovered without sequelae). No MenB infections occurred among vaccinated persons.

Conclusions: Most AEs reported were non-serious and were consistent with those observed in controlled clinical trials of this vaccine. The rate of appendicitis in the vaccinated cohort was consistent with the expected baseline age-specific incidence rate in the US. Post-vaccination syncope has previously been described in younger adolescents; here, we documented the incidence in a college-age population. Measures to prevent injury from syncope and to treat anaphylaxis should be available wherever vaccines are administered. This safety evaluation identified no AEs with lasting sequelae and supports the use of 4CMenB in response to outbreaks.

311. Immunocompromising medications and conditions among patients with severe Streptococcus pneumoniae infections

Jacob B Morton,[1,2] Haley J Morrill,[1,2] Aisling R Caffrey,[1,2] Kerry L LaPlante.[1,2,3] *[1]Infectious Diseases Research Program, Providence VA Medical Center, Providence, RI, USA [2]College of Pharmacy, University of Rhode Island, Kingston, RI, USA [3]Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, RI, USA*

Background: Infections caused by *S. pneumoniae* contribute significantly to the morbidity and mortality of older adults. Immunocompromising (IC) medications and conditions in this population have not been fully elucidated.

Objectives: The purpose of this study was to describe IC conditions and IC medication use among a national cohort of patients with severe (bacteremia, meningitis, and pneumonia) pneumococcal infection.

Methods: This was a retrospective cohort study of older veterans (≥50 years) with positive *S. pneumoniae* cultures (blood, CSF, and respiratory) during admissions to Veterans Affairs Medical Centers between 2002 and 2011. Using diagnosis codes, IC conditions (e.g., solid tumors and hematologic malignancies) were identified at the time of infection. We assessed the use of IC medications (e.g. corticosteroids, monoclonal antibodies, and antineoplastics) at the time of positive culture and the previous 30 days. Differences in patient characteristics, including history of pneumococcal vaccination, were assessed using χ^2 or Fisher's exact tests as appropriate.

Results: There were 14 511 episodes of severe pneumococcal infections identified by positive culture. IC medication use was observed in 67% ($n=9780$) of patients, with 88% ($n=8638$) of those receiving corticosteroids. IC conditions were found in 36% of patients. Pneumococcal vaccination rates were higher in patients with IC medications than non-immunocom promised patients at all time periods evaluated prior to culture date (1 year: 8.6% vs 7.1%, $p=0.013$; 5 years: 32.7% vs 21.1%, $p<0.0001$; 10 years: 39.6% vs 24.8%, $p<0.0001$; overall: 57.3% vs 41.3%, $p<0.0001$). Vaccination rates in patients with IC conditions were not significantly different at 1, 5, and 10 years before culture date, but the overall vaccination rate was lower compared with non-immunocompromised patients (35.3% vs 41.3%, $p<0.0001$).

Conclusions: Patients receiving IC medications were more likely to have received the pneumococcal vaccine than patients without IC conditions or medications, but overall vaccination rates were still low. Efforts should be made to improve vaccination rates in immunocompromised patient populations.

312. Near 'real-time' vaccine safety surveillance using electronic health records – a systematic review of statistical methods

Andreia H Leite,[1] Nick J Andrews,[2] Sara L Thomas.[1] *[1]Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK [2]Statistics, Modelling and Economics Department, Public Health England, London, UK*

Background: Prelicensure studies have limited ability to detect rare adverse events (AE) to vaccines, thus requiring timely post-licensure studies. Near 'real-time' vaccine safety surveillance using electronic health records (EHR) has emerged as an option for identifying safety signals. A review of studies using this approach is important to inform development of similar systems for countries considering their introduction.

Objectives: The objective was to review the methods currently used for near 'real-time' vaccine safety surveillance using EHR.

Methods: Medline, EMBASE and Web of Science were searched, along with citation searches and handsearching of conference abstract books. A questionnaire was also sent to organisations worldwide to ascertain unpublished studies. Eligible studies needed to use EHR and regularly assess pre-specified AE to ≥1 vaccine(s). The characteristics of these studies were determined.

Results: Full results will be presented at the conference. We provide here results from the published literature. From 2773 titles, 22 studies were included from the USA (18), the UK (3) and Taiwan (1). Twenty-eight different vaccines were studied, focusing mainly on influenza (57.1%), especially the 2009 H1N1 vaccines. Depending on frequency of EHR updates and the AE studied, 37 distinct analytic approaches were used. Poisson-based maximized sequential probability ratio test was the most common (37.8%), followed by the binomial version (18.9%) and group sequential tests (10.8%). Twenty-six studies (70.3%) mentioned control for confounding, using an expected rate adjusted for confounding (38.5%), stratification (19.2%) or a combination of self-controlled case series and stratification (15.4%). One-hundred twenty-six potential AE were evaluated, most frequently Guillain–Barre syndrome, seizures and serious allergic reactions (11.9% each).

Conclusions: Near 'real-time' vaccine safety surveillance using EHR is a developing field, mainly used to evaluate influenza vaccines, in a limited number of countries. Choice of the method has been guided by frequency of EHR updating and the AE studied. Expert contacts are ongoing to complement these results, which in turn will inform the setup of new systems.

313. Key features of vaccine reports in VigiBase

Lovisa Sandberg, Jonas Fransson, Kristina Juhlin, Kristina Star, Rebecca Chandler. *Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden*

Background: Worldwide individual case safety reports (ICSRs) of adverse events (AEs) are collected in the WHO global ICSR database, VigiBase®. Approximately 10% of the reports in the database concern vaccines. Characterizing these reports will serve as a basis for vaccine-specific signal detection in VigiBase.

Objectives: The aims of the study were to characterize and identify key features of vaccine reports in VigiBase.

Methods: Vaccine ICSRs, i.e. reports with at least one suspected vaccine (ATC J07), were retrieved and compared with all other reports in VigiBase as of May 2013. Descriptive statistics for country of origin, patient demographics, reported drugs and type of AEs were obtained. VigiPoint, a method for open-ended pattern discovery based on shrinkage odds ratios (OR), was used to identify the key features defined as covariate values or ranges for which the absolute value of the 99% confidence interval of the shrunk $\log_2$ OR was above 0.5.

Results: A total of 753 000 vaccine reports and 7 243 000 other reports were included in the analysis. Reporting of vaccine AEs to VigiBase has increased over time and vaccine reports originated from 97 out of 106 countries reporting to VigiBase at the time of data extraction. A higher than expected number of vaccine reports compared with other reports were observed for North America (64% vs. 54%) and Oceania (6% vs. 4%), especially for Canada and New Zealand; the opposite pattern was noted for Asia (2% vs. 10%) and Latin America (1% vs. 2%). Top reported highlighted vaccines were DTP, influenza, MMR and polio vaccine; AEs were fever, various injection site reactions and crying abnormal (WHO-ART preferred term level). Other key features included higher than expected number of vaccine reports for individuals aged 0–17 years (62% vs. 8%) and lower than expected number of vaccine reports for fatal outcomes (1% vs. 6%).

Conclusions: Individuals of young age and events indicative of non-serious nature were identified the key features that distinguish vaccine reports from other reports in VigiBase. The variation in vaccine reporting by geographical regions is a noteworthy feature to consider when performing analyses in VigiBase.

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314. Risk of anaphylaxis following vaccination in children and adults

Michael M McNeil,[1] Eric Weintraub,[1] Jonathan Duffy,[1] Lakshmi Sukumaran,[1] Steven J Jacobsen,[2] Nicola P Klein,[3] Simon J Hambidge,[4] Grace M Lee,[5] Lisa A Jackson,[6] Stephanie A Irving,[7] Jennifer P King,[8] Elyse O Kharbanda,[9] Robert A Bednarczyk,[10] Frank DeStefano.[1] *[1]CDC, Atlanta, GA, USA [2]Southern California Kaiser Permanente, Pasadena, CA, USA [3]Kaiser Permanente Vaccine Study Center, Oakland, CA, USA [4]Institute for Health Research Kaiser Permanente, Denver, CO, USA [5]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA [6]Group Health Research Institute, Seattle, WA, USA [7]Center for Health Research Kaiser Permanente Northwest, Portland, OR, USA [8]Marshfield Clinic Research Foundation, Marshfield, WI, USA [9]HealthPartners Institute for Education and Research, Minneapolis, MN, USA [10]Kaiser Permanente Center for Health Research and Emory University, Atlanta, GA, USA*

Background: Anaphylaxis is a potentially life-threatening allergic reaction. The risk of anaphylaxis following vaccination has not previously been well described in adults or with newer vaccines in children.

Objectives: The aimed was to estimate the incidence of anaphylaxis following vaccines recommended in the United States.

Methods: Using healthcare data from the Vaccine Safety Datalink (VSD), we determined rates of anaphylaxis following vaccinations in children and adults. We first identified all patients with a vaccination record during January 2009 to December 2011 and used diagnosis and procedure codes to identify potential cases of anaphylaxis. Medical records of potential cases were reviewed. Confirmed cases met the Brighton Collaboration definition of anaphylaxis levels 1 and 2. We calculated the incidence of anaphylaxis following all vaccines combined and for selected individual vaccines.

Results: We identified 33 confirmed post-vaccination anaphylaxis cases that occurred following 25, 173 and 965 vaccine doses. The rate of anaphylaxis was 1.31 per million vaccine doses (95%CI [0.90, 1.84]). The incidence did not vary significantly by sex or age. Vaccine-specific rates were highest for HZV 9.60 (95%CI [1.16, 34.67]) per million doses and rabies vaccine 86.1 (95%CI [2.18, 479.43]) per million doses; however, these were based on two cases and one case, respectively, in whom the vaccine was given alone. A majority (85%) of the cases had a prior history of atopy. All case patients recovered; a minority (45%) received epinephrine treatment.

Conclusions: Anaphylaxis following vaccinations is rare in all age groups. Providers nonetheless need to be alert to this life-threatening medical emergency, particularly in known atopic patients, and ensure availability of epinephrine and procedures for emergency management.

315. Incidence of outcomes relevant to vaccine safety monitoring in a large commercially insured population

Daina B Esposito,[1] Lina Titievsky,[2] Jennifer CL Hawes,[3] Rosalind C Hollingsworth,[2] Daniel A Scott,[2] Crystal N Holick,[1] Stephan Lanes.[1] *[1]Safety and Epidemiology, HealthCore, Inc., Andover, MA, USA [2]Pfizer Inc., New York, NY, USA [3]Aetion, Inc, New York, NY, USA*

Background: Potential safety signals arise during the life cycle of a vaccine from pre-marketing trials, spontaneous post-marketing reports and published case reports. Analysis of a pre-established "standing cohort" to monitor background incidence rates of select outcomes can inform the evaluation of potential safety signals.

Objectives: The stuyd aimed to estimate the incidence rate (IR) of conditions relevant for vaccine safety monitoring within the population for which 13-valent pneumococcal conjugate vaccine (Prevnar 13®, PCV13) is indicated and/or ACIP recommended.

Methods: We identified patients aged 6–100 years not vaccinated with PCV13 but with at least 1 year of continuous health plan eligibility in the HealthCore Integrated Research DatabaseSM. Baseline characteristics were established in the first year of health plan eligibility, and 36 outcomes of interest were pre-specified. IRs were calculated as the number of incident events divided by the total person-time at risk; stratified by age, gender, and risk of invasive pneumococcal disease (IPD); and presented with a 95% confidence interval (CI).

Results: We followed 16 763 765 commercially insured individuals for a mean of 2.4 years (SD 1.82). IRs (per 100 000 person years) were greatest for asthma/wheezing: 822.9 (95%CI [820.0, 825.8]), ischemic cardiac events: 652.7 (95%CI [650.1,

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655.3]), hypothyroidism: 488.6 (95%CI [486.3, 490.8]), and type 2 diabetes mellitus: 383.3 (95%CI [381.3, 385.3]). IRs for thyroid, allergic/autoimmune, and hematologic conditions were greater in women than men. IRs of nephrotic, cardiac, and metabolic outcomes were slightly greater in men. Most IRs increased with age, and all IRs were highest in patients at high risk for IPD.

Conclusions: The study provides background rates for 36 different outcomes estimated in the population indicated for (or recommended to receive) PCV13. Our results provide context for evaluating potential safety signals that might be reported in exposed individuals and the populations in which they are likely to occur. Deviations from background patterns could warrant further investigation.

316. Use of the high-dose influenza vaccine among commercially insured patients in the United States, 2010–2012

Leah J McGrath,[1,2] M Alan Brookhart.[2] *[1]RTI Health Solutions, Research Triangle Park, NC, USA [2]University of North Carolina - Chapel Hill, Chapel Hill, NC, USA*

Background: High-dose inactivated, influenza vaccine was licensed in the United States in December 2009 for adults aged 65 years and older. National recommendations do not include a preference for a specific influenza vaccine in the elderly population. The extent of its use is unknown.

Objectives: The study aimed to measure and characterize the on-label and off-label use of high-dose influenza vaccine among commercially insured Americans.

Methods: Using the MarketScan Commercial Claims and Encounters and the Medicare Supplemental database, we identified individuals who received the high-dose influenza vaccine or the standard, seasonal trivalent influenza vaccine between 1 January 2010 and 31 December 2012. For people aged ≥65 years, we used multivariable regression to assess the association between patient- and provider-level variables and high-dose influenza vaccine versus standard influenza vaccine. Off-label vaccination was defined as high-dose vaccine administered to people younger than 65 years of age. We examined the association between various comorbid conditions and receipt of the high-dose vaccine among adults aged 18–64 years.

Results: Among patients aged ≥65 years who received an influenza vaccine, 18.4% received the high-dose vaccine. Uptake was minimal in 2010, but 25% and 32% of the administered influenza vaccines were the high-dose formulation in 2011 and 2012, respectively. Almost 27 000 seniors received a second high-dose vaccine with a median of 368 days (IQR: 350–387 days) between doses. Older age and seeing a family practice physician were positively associated with receiving high-dose vaccine. There were 36 624 off-label high-dose vaccines administered. Half of the patients receiving off-label doses were aged 50–64 years. Adults aged 18-64 years receiving high-dose vaccine were more likely to have chronic comorbidities than adults receiving standard influenza vaccine.

Conclusions: In the first 3 years since licensure, use of the high-dose vaccine among seniors has been limited. The safety of this vaccine should be monitored among seniors receiving repeat doses and off-label vaccine recipients younger than 65 years.

317. Effectiveness of influenza vaccination for children in Japan

Natsumi Shibata,[1] Hisashi Urushihara.[2] *[1]Drug Development and Regulatory Science, Faculty of Pharmacy, Keio University, Tokyo, Japan [2]Drug Development and Regulatory Science, Faculty of Pharmacy, Keio University, Tokyo, Japan*

Background: The morbidity of influenza is higher in children than adults. Influenza vaccination in children has been shown to effectively prevent the onset and spread of influenza in the community. To date, however, no large-scale comparative study has examined the effectiveness of influenza vaccine in Japan.

Objectives: The aim of the study was to evaluate the effectiveness of influenza vaccination in children aged 1–15 years in Japan.

Methods: We conducted a cohort study using a large-scale medical claims database, which included more than three-million insured persons covered by the Employees' Health Insurance Program. Records for influenza vaccination subsidy by company insurance were used to identify subjects receiving vaccination. Primary analysis was to evaluate the effect of influenza vaccination on preventing influenza, based on the diagnosis codes in ICD10 with/without rapid-testing results. Secondary analysis was to evaluate the effect of

influenza vaccination on the incidence of related respiratory tract diseases, such as pneumonia. Potential risk covariates were adjusted for by binary logistic regression.

Results: In the 2012 influenza season, 30 197 children were included in the primary analysis. Vaccination rate was 50.4% overall. Average age was 7.18 years, and each age group had over 1000 children; 48.6% children were female. Primary odds ratio (OR) for influenza recorded in ICD10 codes was 0.823 for vaccinees (95%CI [0.766, 0.883]). Similar OR was yielded with rapid-testing results, confirming the robustness of the result. Stratification by age revealed significant vaccine effectiveness in infants aged under 5 years, except in those aged 3 years, and in 8 year old. A significant gender difference in influenza occurrence was detected (female vs male, OR: 0.904; 95%CI [0.853, 0.958]). Additionally, secondary analysis revealed that influenza vaccination significantly reduced the risk of pneumonia diagnosis (OR for vaccines: 0.710; 95% CI [0.600, 0.839]).

Conclusions: In the 2012 influenza season, influenza vaccination significantly prevented the onset of influenza, particularly for infants aged under 5 years. Further, influenza vaccination was effective in reducing related respiratory complications.

318. Active monitoring of local inflammations within a cohort of patients vaccinated with influenza vaccine

Leontine HW van Balveren, Agnes C Kant, Linda VDH Härmark. *Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands*

Background: The Netherlands have developed a web-based active monitoring system where patients, vaccinated with influenza vaccine, can report the occurrence of adverse events following immunisation (AEFI). Local inflammation is the most reported AEFI after influenza vaccination. A local reaction with at least two criteria for inflammation is diagnosed as 'injection site inflammation' (ISI). If the reaction extends over a joint or around the limb, it concerns 'extensive limb swelling' (ELS).

Objectives: In this study, we focused on reported ISI and ELS. The objective was to evaluate whether additional questions concerning local inflammations provide more insight into the characteristics and severity of ISI and ELS.

Methods: After influenza vaccination, patients received three questionnaires concerning AEFI at set time points within 30 days. If reporting an ISI or ELS, patients received an additional questionnaire within 4 days to examine the localisation, symptoms and severity of the local inflammation. Initial ISI and ELS were verified to the characteristics reported in the additional questionnaire. The characteristics and severity of the inflammations were summarised.

Results: The cohort consisted of 1401 patients. One-hundred ninety-seven patients reported a local inflammation (ISI 185/ELS 12). Of these, 180 (93.8%; 171 ISI/9 ELS) completed the additional questionnaire. Based on the additional questions, the diagnosis was divergent in 11.7% reports from the initial diagnosis, and ELS and ISI were respectively defined as ISI (66.7%) and ELS (5.3%). Most reported symptoms were pain (162) and redness (158). Three patients visited a physician. Most patients had no or slight problems with daily activities. Twenty-six patients reported slight (9) or moderate (14) problems with sleeping pose.

Conclusions: The response rate to the additional questionnaire was high. Given the short time between both questionnaires, recall bias was probably minimalized. There was a difference in ISI and ELS diagnoses. The additional questions provided us more information concerning symptoms, localisation and severity of ISI and ELS. Active monitoring of reported ISI and ELS is a valuable tool in vaccine vigilance.

319. Effectiveness of seasonal influenza vaccines against influenza A (H1N1) infection in post-pandemic seasons: a systematic review

Songul Bozat-Emre, Natalie Casaclang, Hasantha C Sinnock, Xibiao Ye, Salaheddin M Mahmud. *Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada*

Background: Effectiveness of the seasonal influenza vaccines in preventing influenza A (H1N1) strain, A (H1N1)pdm09, in post-pandemic seasons remains controversial despite many epidemiological studies.

Objectives: We aimed to conduct a systematic review of epidemiological studies to summarize the epidemiologic evidence on the effectiveness of seasonal influenza vaccines against A(H1N1)pdm09 infection in post-pandemic seasons.

Methods: We searched multiple computerized literature databases for studies published from 1st January 2010 to 31st March 2014.The outcome was laboratory-confirmed A(H1N1)pdm09 infection, and the exposure was receipt of seasonal influenza vaccines. All the studies met our inclusion criteria were reviewed by two researchers independently (NC&SBE). Information extracted from all identified studies included study country, study design, study population, outcomes, confounders adjusted for in analyses, and estimates of vaccine effectiveness and associated confidence intervals (95%CI).

Results: We identified 27 eligible studies, with majority of the studies conducted in 2010/2011 influenza season ($n = 18$). Among general population, seasonal influenza vaccines had 40–80% effectiveness in preventing A(H1N1)pdm09 virus, depending on age group, influenza season, and study country. The corresponding estimates were 36–63% among high-risk population and 34–58% among hospitalized population. Overall, seasonal influenza vaccine effectiveness was the highest among pediatric population (59–87%) and in North America (59–80%) and Australia (78%).

Conclusions: The current epidemiological evidence suggests the effectiveness of seasonal influenza vaccines in preventing A(H1N1)pdm09 infection in post-pandemic seasons, especially among pediatric population.

320. Influenza vaccine utilization: a comparison between urban and rural counties in Florida

Abdullah Abdulaziz Alalwan,[1] Xiaohui Xu,[2] Abraham Hartzema.[1] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA [2]Department of Epidemiology, University of Florida, Gainesville, FL, USA*

Background: The World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend that every person aged 6 months and over receives the influenza vaccine every year. Previous studies indicate that rural-area residents have less access to preventative health care services. Furthermore, underutilization of the influenza vaccine has been reported in several studies. This study examines the variation in influenza vaccine use among rural and urban counties in Florida.

Objectives: The study aimed to determine the impact of living in rural or urban counties on the utilization of influenza vaccine across Florida.

Methods: The study studied 24 116 participants from the Behavioral Risk Factor Surveillance System database. The study included only patients who live in Florida. We performed logistic regression analysis using survey procedures available in SAS®. Our regression model assessed the association between receiving the influenza vaccine and county status, age, income level, education level, and health coverage. We used ArcGIS software to create prevalence and vaccination maps.

Results: Of the total number of the study participants, 45.31% were residents of rural counties, and 54.69% were residents of urban counties. The logistic regression model showed no significant association between residing in rural counties and not receiving influenza vaccine in the past year (-0.05560, p-value 0.0549). However, we found significant associations between not receiving influenza vaccine and age, high education level, and not having health care coverage (-0.0412, p-value < 0.0001; -0.04462, p-value 0.0139; and 0.4956, p-value < 0.0001, respectively).

Conclusions: Our study did not find an association between influenza vaccine use among rural and urban residence. Increasing age, higher education, and having health care insurance had positive associations with influenza vaccine use.

321. Reduction of influenza disease cost with suboptimal vaccination

Nicole M Bailey, Andrew Wilson, Yongmei Li, Aaron Kamauu. *Anolinx, LLC, Salt Lake City, UT, USA*

Background: The burden of disease due to seasonal influenza in the United States (US) remains high, despite vaccination efforts. In 2003, it was estimated that the direct medical costs averaged $10.4 billion, with a total economic burden estimated at $87.1 billion.

Objectives: Although the seasonal influenza vaccination is not always a consummate match, we suggest that the burden of disease is still greatly reduced even when vaccine match to circulating strain is suboptimal. This study aims to examine the decreased cost burden associated with the seasonal influenza vaccine, even in

seasons of suboptimal match, by comparing historic published trends to large claims data.

Methods: Previously published data were compared to seasonal influenza records, queried from a claims database containing over 55 million unique patients. Regression modeling was used to compare cost burden of persons unvaccinated with the seasonal influenza vaccine and persons vaccinated during seasons where vaccine was considered (by the CDC-reported vaccine effectiveness percentage (VE% = (1-relative risk)*100%)) a suboptimal match for seasonal flu strain.

Results: Published vaccine effectiveness for a suboptimal seasonal influenza vaccination ranged from 39% to 63% from flu seasons 2006–2007 to 2013–2014. This was approximately the same protection observed in the large claims database for the same year ranges. When modeled together with cost, it was shown that this mismatch of vaccination to circulating virus still equated to a substantial reduction in burden of disease when vaccinated. Validation of results is still ongoing.

Conclusions: The burden of disease of influenza significantly decreases even when the seasonal influenza vaccine is a suboptimal match to the prevalent circulating strain. It is recommended that all persons able to receive the influenza vaccination do so, whether or not the match is optimal. It has been demonstrated that a suboptimal match effectively decreases the burden of the disease.

322. Post-licensure surveillance of quadrivalent live attenuated influenza vaccine United States, vaccine adverse event reporting system (VAERS), July 2013–June 2014

Penina Haber, Pedro L Moro, Maria Cano, Paige Lewis, Brock Stweart, Tom T Shimabukuro. *CDC, Atlanta, USA*

Background: Quadrivalent live attenuated influenza vaccine (LAIV4) was approved in 2012 for healthy persons aged 2–49 years. Beginning with the 2013–2014 influenza season, LAIV4 replaced trivalent live attenuated influenza vaccine (LAIV3).

Objectives: The study aimed to analyze LAIV4 reports to VAERS and compare with LAIV3 VAERS reports from recent previous influenza seasons.

Methods: We analyzed LAIV4 reports to VAERS, a national spontaneous reporting system. Medical records were reviewed for non-manufacturer serious reports (i.e., death, hospitalization, prolonged hospitalization, life-threatening illness, and permanent disability) and reports of selected conditions of interest. We conducted Empirical Bayesian data mining to identify disproportional reporting for LAIV4.

Results: In 2013–2014, 12.7 million doses of LAIV4 were distributed, and VAERS received 779 reports in individuals aged 2–49 years; 95% were non-serious. Expired drug administered (42%), fever (13%), and cough (8%) were the most commonly reported in children aged 2–17 years when LAIV4 was administered alone, while headache (18%), expired drug administered (15%), and exposure during pregnancy (12%) were the most common in adults aged 18–49 years. We identified one death report in a child who died from complications of cerebellar vascular tumors. Among non-death serious reports, neurologic conditions were common in children and adults. In children, seizures (3) and Guillain–Barré syndrome (2) were the most common serious neurologic outcomes. We identified three serious reports of asthma/wheezing following LAIV4 in children. Data mining detected disproportional reporting for vaccine administration errors and for influenza illness in children.

Conclusions: Our analysis of VAERS reports for LAIV4 did not identify any concerning patterns. The data mining finding for reports of influenza illness is consistent with low LAIV4 vaccine effectiveness observed for influenza A disease in children in 2013–2014. Reports of LAIV4 administration to persons in whom the vaccine is not recommended (e.g., pregnant women) indicate the need for education, training, and screening regarding indications.

323. Safety of seasonal influenza vaccines in pregnancy in the vaccine adverse event reporting system, 2010–2014

Pedro L Moro,[1] Paige Lewis,[1] Janet Cragan,[2] Naomi Tepper.[3] *[1]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA, USA [2]Birth Defects Branch, Division of Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA [3]Women's Health and Fertility Branch, Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, GA, USA*

Background: Routine immunization of pregnant women with inactivated influenza vaccines (IIV) is recommended in all trimesters of pregnancy. A review of VAERS during 1990–2009 did not find any unexpected patterns of pregnancy complications or fetal outcomes after administration of inactivated influenza (IIV) or live attenuated influenza vaccines (LAIV). However, during 2009–2010, VAERS reports from pregnant women who received the influenza A (H1N1) 2009 monovalent vaccine increased.

Objectives: The study aimed to assess the safety of seasonal influenza vaccines in pregnant women and their infants whose reports were submitted to VAERS during 2010–2014 because of the increased reporting observed during the 2009–2010 pandemic H1N1 vaccination campaign.

Methods: We searched the VAERS database for US reports of adverse events (AEs) in pregnant women who received IIV or LAIV vaccines from 1 July 2010 to 30 June 2014. Clinicians reviewed reports and available medical records and assigned each report a primary clinical category.

Results: We found 389 reports after seasonal influenza vaccines administered to pregnant women; 311 were after IIV and 78 after LAIV. In 91 (40%) reports, IIV was administered during the first trimester; 44 (11%) reports were serious; no deaths were reported. Among IIV reports, the most frequent pregnancy-specific AE was spontaneous abortion in 50 (16%) reports, followed by premature delivery in five (2%). Neonatal or infant outcomes were reported in 11 (3.5%) reports, which included five major birth defects of multiple different types and no neonatal deaths. Among LAIV reports, only 9/78 reported an AE.

Conclusions: This review of VAERS reports following seasonal influenza vaccines in pregnancy found no new or unexpected patterns in maternal or fetal outcomes.

324. Pattern of quadrivalent human papillomavirus vaccine (HPV4) use among insured males in the United States: 2009–2013

Kandace L Amend,[1] Bruce Turnbull,[1] Michael Doherty,[1] Mark Marsico,[2] Christine Velicer,[2] Patricia Saddier,[2] John Seeger.[3] *[1]Epidemiology, Optum, Waltham, MA, USA [2]Epidemiology, Merck Sharp and Dohme, Corp., Whitehouse Station, NJ, USA [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA*

Background: The quadrivalent human papillomavirus vaccine (HPV4) – Gardasil® – was approved in the US for females in 2006 and expanded for use in males in October 2009 for the prevention of HPV-related anogenital diseases. Labeled to be administered in three doses over 6 months, the use of HPV4 in females has been described well, but usage patterns in males have not.

Objectives: The study aimed to describe the patterns of HPV4 dosing among commercially insured US males.

Methods: Using a large national health insurance claims database, we identified males vaccinated with HPV4 by its specific procedure code (Current Procedural Terminology (CPT) 90649). Subsequent doses of HPV4 (Dose 2 and Dose 3) were similarly identified, and the time from first dose to each subsequent dose was determined. A cumulative dosing curve was constructed with follow-up time in months as the timescale.

Results: Between October 2009 and December 2013, a total of 65 025 males received a first dose of HPV4, 33 105 (51%) received a second dose, and 14 434 (22%) received a third dose. These crude percentages at each dose do not account for changes in the denominator due to disenrollment. The majority of males (89%) receiving HPV4 were between 11 and 18 years old at first dose. Of those receiving three doses of the vaccine, 75% (10 822 of 14 434) did so within the labeled time intervals. Increases in receipt of subsequent doses were observed at 12 and 24 months after Dose 1. There was also an increase in doses in the third calendar quarter compared to other times in the year. Receipt of subsequent doses continued for more than 2 years after Dose 1: of males who received Dose 2, 55% did so within 12 months and 69% within 24 months; of those who received Dose 3, 27% did so within 12 months of Dose 1 and 41% within 24 months.

Conclusions: Use of HPV4 appears low in adolescent males in this representative US-insured population, and timing of subsequent doses suggests that they are often given at annual physician office visits, suggesting opportunities to improve timely completion of the HPV4 regimen in males.

325. Factors Predicting Human Papillomavirus Vaccination Intention and Uptake: A Meta-analysis and Systematic Review

Andrew R Wilson,[1,2] Mia Hashibe,[1,3] Lisa H Gren,[1] Chang-Chung Chou,[1] Anna T Gardener,[1] Jessica Greenwood,[1] Brian R Jackson,[4,5] Rosemary She,[6] Deanna Kepka,[3,7] Nicole Bailey,[1,2] Marlene J Egger.[1]
[1]Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, USA; [2]Health Data Analytics, Anolinx, Salt Lake City, UT, USA; [3]Cancer Control and Population Sciences, Huntsman Cancer Institute, Salt Lake City, UT, USA; [4]ARUP Laboratories, Salt Lake City, UT, USA; [5]Department of Pathology, University of Utah, Salt Lake City, UT, USA; [6]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [7]College of Nursing, University of Utah, Salt Lake City, UT, USA.

Background: Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide and is the primary cause of cervical and other cancers. Despite the availability of effective vaccines, vaccination rates remain low. Many studies predicting vaccination intention exist, but few studies exist to synthesize the many findings.

Objectives: The purpose of this study is to examine physicians' intentions to prescribe, individual and parental intention to vaccinate, and predictors of intention to receive the HPV vaccine.

Methods: Our database search strategy identified 1269 studies relating to physician recommendation, parental and individual intention, uptake, and factors relating to individual intention to receive the HPV vaccine. Three reviewers independently abstracted data, and discrepancies were resolved by consensus between abstractors. Subgroup analysis and meta-regression analysis were performed to investigate and reduce heterogeneity where heterogeneity was high.

Results: Of the 1269 articles identified through database searches, 456 abstracts were reviewed and 306 were relevant. Of these, 74 were included in the final analysis.

For studies that considered physician recommendation, physicians were very likely to recommend or prescribe the HPV vaccine. However, this proportion varied significantly by the age category of the intended recipient, with physicians more likely to recommend or prescribe to older children and more likely still to recommend or prescribe for adults.

We also summarized parental intention to vaccinate children, individual's intention to vaccinate themselves, vaccine uptake, and odds ratios of factors predicting parental and individual intention to vaccinate and vaccine uptake.

Conclusions: Despite the ACIP recommendations for routine HPV vaccination of females aged 11 or 12 years and catch-up vaccination for females aged 13 through 26 years, we found that physicians are more likely to recommend vaccination at later ages.

Additionally, findings on parental and individual intent and uptake and factors that drive them might better inform future interventions aimed at increasing HPV vaccination rates.

326. Validation of Current Procedural Terminology Codes for Rotavirus Vaccination in Two Commercially Insured US Populations

Veena Hoffman,[1] Nicholas J Everage,[2] Scott Quinlan,[3] Kathleen Skerry,[2] Daina Esposito,[3] Nicolas Praet,[4] Dominique Rosillon,[4] Crystal N Holick,[3] David D Dore.[2]
[1]Epidemiology, Optum, Ann Arbor, MI, USA; [2]Epidemiology, Optum, Waltham, MA, USA; [3]HealthCore, Inc., Wilmington, DE, USA; [4]GSK Vaccines, Wavre, Belgium.

Background: The Current Procedural Terminology (CPT) code designated for billing for the live, oral, pentavalent rotavirus vaccine (RV5; CPT 90 680) differs by one digit from the code for the live, oral, human rotavirus vaccine (RV1; CPT 90 681). One code may be mistakenly substituted for the other in health insurance claims, resulting in exposure misclassification in studies that differentiate between RV5 and RV1.

Objectives: We present the final results of a validation study to quantify the validity of codes used in health insurance claims to bill for rotavirus vaccines.

Methods: Rotavirus vaccination claims bearing codes for RV5 or RV1 were randomly sampled from an ongoing cohort study of infants less than 1 year of age identified from two large US health plans between August 2008 and March 2013. Within the sample, we compared the CPT code from the claims with the vaccine recorded in medical records obtained from providers who submitted the claims and estimated the positive predictive values (PPVs) of the respective claims.

Results: We confirmed that 92 of 104 RV1 claims (PPV: 88.5%; 95%CI: 80.7–93.9%) and 98 of 113

RV5 claims (PPV: 86.7%; 95%CI: 79.1–92.4%) were correctly classified. Three RV1 claims corresponded to RV5 administration and were thus misclassified. No RV5 claims were confirmed as RV1 in the medical record. Nine RV1 and 15 RV5 claims were not confirmed because of insufficient information in the medical record to classify rotavirus vaccine type.

Conclusions: Rotavirus vaccine appears to be correctly coded in most circumstances within health plan claims data. The PPVs reported here represent lower bounds of plausible values as those with insufficient information in the medical records were excluded from the numerator but included in the denominator of the PPV calculations.

327. Intussuception after Rotarix Vaccien Adverse Event Reporting System (VAERS0, 04/2008–12/2014)

Penina Haber, Umesh D Parashar, Eric S Weintraub, Michael J Haber, Frank DeStefano. *ISO, CDC, Atlanta, GA, USA; Bio Statistics, Emory University, Atlanta, GA, USA.*

Background: In 2008, a new oral monovalent human rotavirus vaccine (RV1, Rotarix®, GlaxoSmithKline Biologicals) was introduced in the United States. RV1 was associated with intussusception in a recent US active surveillance study at a rate of five excess cases per 100 000 vaccinated infants, but these data were based on only six intussusception reports in the risk window during the first week after vaccination.

Objectives: The aim of this study was to assess intussusception events reported during April 2008–December 2014, using VAERS data.

Methods: VAERS is a US national spontaneous postlicensure vaccine safety surveillance system. Intussusception reports were confirmed using Brighton case definition level 1. We conducted a self-controlled risk interval analysis using Poisson regression to estimate the daily reporting ratio (DRR) of intussusception, comparing rates of daily reports 3–6 days (risk period based on timing of peak viral replication and data from other studies) versus 0–2 days (control period) after vaccination, assuming it is unlikely that vaccine-related intussusception occurs so soon after vaccination. We calculated reporting rate differences based on DRRs and background rates of intussusception.

Results: Between 1 April 2008 and 31 December 2014, VAERS received 1103 adverse event reports following RV1 vaccinations, including 112 intussusception reports, of which 108 (98%) were confirmed. Of the 108 confirmed intussusception events, 61 (56%) occurred after dose 1, 41 (38%) after dose 2, and although not recommended, 7 (6%) were reported after a third dose. During the same time period, 10.9 million RV1 doses were distributed in the USA. The DRR comparing days 3–6 with days 0–2 after dose 1 was 7.5 (95%CI = 2.3, 24.6) and 2.4 (95% CI = 0.8, 7.5) after dose 2. Over both doses, the excess risk of intussusception was 2.3 events (95% CI = 0.8,7.1) per 100 000 vaccinations.

Conclusions: We observed an increased risk of intussusception events 3–6 days after dose 1 of RV1 vaccination compared with days 0–2. This increased risk could translate to a small increased risk of intussusception comparable with that reported in other studies.

328. Clinical and Demographic Characteristics of an Expanded Target Population for 13-Valent Pneumococcal Conjugate Vaccine (Prevnar 13®, PCV13)

Lina Titievsky,[1] Daina B Esposito,[2] Jennifer CL Hawes,[2] Robert Maroko,[1] Rosalind C Hollingsworth,[1] Crystal N Holick,[2] Stephan Lanes.[2] *[1]Pfizer, Inc., New York, NY, USA; [2]HealthCore, Inc., Andover, MA, USA.*

Background: PCV13 is approved for children aged 0–5 years (2010) and 6–17 years (2013). The ACIP recommends PCV13 for those ≥19 years with medical conditions increasing their risk of IPD.

Objectives: The aim of this study was to describe the target population for PCV13 with respect to demographic and clinical characteristics.

Methods: We identified individuals aged 6–100 years with at least 1 year of continuous health plan eligibility in a large, commercially insured US population (HealthCore Integrated Research Database[SM], 2007–2013). We characterized the study population according to key characteristics and the top 30 most reported diagnoses, procedures, and dispensed medications during the baseline (i.e., 1st year of health plan eligibility) and follow-up. We summarized the data using counts and percentages for categorical variables and mean, median, and standard deviation (SD) for continuous variables.

Results: There were 16.7 million individuals that met the eligibility criteria. The mean age of cohort members was

37.9 years (SD = 18.40) with a mean follow-up duration of 2.4 years. In those aged 6–18 years, diagnoses in the baseline year reflected routine preventive care, common infections (11%), and symptoms such as acute pharyngitis (18%) and acute sinusitis (7%), whereas in adults, these included routine exams and screening, hyperlipidemia (13%), hypertension (13%), and symptoms (pain (12%), diabetes (7%), and various infections). The most frequent procedures in 6–18 years included vaccinations and laboratory tests and psychiatric/counseling encounters, and in adults, these were routine venipuncture, laboratory tests, and radiologic imaging. The most commonly dispensed medications were antibiotics, opioids, and anti-asthmatic agents in 6–18 years and opioids in adults.

Conclusions: This study describes demographic and clinical characteristics of the sub-populations likely to become vaccinated with PCV13. These characteristics are relevant for contextualization of potential safety concerns or providing an indication of what sort of adverse events are to be expected.

329. Knowledge, Attitude, and Practice of Healthcare Professionals toward Hepatitis B Vaccine and Disease

Hisham Alshammari,[1] Metab Alenazi,[1] Mohammad Almuslim,[1] Mohamad Aljofan,[1] Thamir Alshammari.[1,2]
[1]Clinical Pharmacy, University of Hail, Hail, Saudi Arabia; [2]Medication Safety Research Chair, King Saud University, Riyadh, Saudi Arabia.

Background: Hepatitis B virus infection is a common disease that affects 1.5 million individuals in the USA and 350 to 400 million worldwide.

Objectives: The aim of this study was to evaluate the level of knowledge and attitude of healthcare professionals in Saudi hospitals toward Hepatitis B virus vaccination.

Methods: Knowledge and attitudes toward Hepatitis B virus vaccination of healthcare professionals from tertiary, secondary, and primary care clinics Saudi Arabia were assessed by a cross-sectional study. Over a 2-month period (November–December, 2014), more than 500 healthcare professionals from different hospitals across seven provinces in Saudi Arabia were surveyed. In addition to demographic data, the distributed surveys consisted of two other parts that focus on the participants' knowledge of the diseases including its risk factors and treatments as well as their attitudes toward the HBV vaccine. Descriptive statistics were used to report responses using Statistical Analyses Software (SAS 9.3). A chi-squared test or Fisher exact tests were used to analyze the categorical data. All statistical tests were conducted with a two-tailed alpha of 0.05.

Results: The overall response rate was 80% with the majority of the participants (81%) stated that they have direct contact with patients or patient fluids on a daily basis. To our shock, 19% of the participants did not know that HBV affects the liver and worse 6% failed to recognize blood as the major transmitting route. Despite the fact that 34% claimed that they have had needle stick injury, of those, 15% believed that healthcare professionals are at no risk of contracting HBV virus, 24% listed HBV vaccine as a cause of the HBV infection and 38% think they can obtain HBV more than once. In addition, 74% of the participants did not have any training or education regarding HBV vaccine.

Conclusions: The majority of the surveyed seem to have little or no knowledge of HBV infection or its treatment. The regulating body in Saudi Arabia is urged to introduce mandatory training for healthcare practitioners on HBV and other common communicable diseases.

330. Current Practices and Regulations in European Countries for Data Privacy and Ethics for the Use of Secondary Data: An ADVANCE Initiative

Helene Denis,[1] Alena Khromava,[1] Harshana Liyanage,[2] Jorgen Bauwens,[3] Lieke Van der Aa,[4] Patrick Mahy,[4] Filipa Ferreira,[2] Alessandro Spina,[5] Germano Ferreira,[6] Miia Artama,[7,8] Kari Natunen,[7] Nynke Rots,[9] Klara Berencsi,[10] Miriam Sturkenboom,[11] Simon de Lusignan.[2]
[1]Global Pharmacovigilance, Sanofi Pasteur Ltd, Toronto, ON, Canada; [2]University of Surrey, Guildford, Surrey, UK; [3]Brighton Collaboration Foundation, Basel, Switzerland; [4]WIV-ISP, Brussels, Belgium; [5]European Medicines Agency, London, UK; [6]GlaxoSmithKline Biologics, Brussels, Belgium; [7]University of Tampere, Tampere, Finland; [8]Finnish Cancer Registry, Helsinki, Finland; [9]Centre for Immunology of Infectious Diseases and Vaccines, RIVM, Bilthoven, The Netherlands; [10]Aarhus University Hospital, Aarhus, Denmark; [11]Erasmus University Medical Centre, Rotterdam, The Netherlands.

Background: The Innovative Medicines Initiative project Accelerated Development of Vaccine benefit-risk Collaboration in Europe (ADVANCE) aims to

establish validated and tested framework that could rapidly provide robust data and scientific evidence on vaccine benefits and risks. Across Europe, access and processing of personal data are guided by the data protection directive (95/46/EC).

Objectives: The aim of this study was to compare privacy and ethics (P&E) practices for access and secondary use of health data in Europe.

Methods: Firstly, feedback was gathered from different data custodians across EU Member States regarding their experiences on legal framework for P&E on the use of secondary data for health research. Secondly, experience on P&E from European projects (ENCEPP, VENICE, EHR4CR and PARENT) were analysed. Finally, ADVANCE International Research Readiness (AIRR) survey was developed and distributed among ADVANCE partners.

Results: Seventeen of 19 database custodians responded to the AIRR survey, covering seven countries and data from 15 506 402 people, registered between 1979 and 2013. Eleven out of 15 (73%) database custodians that answered question had a governance committee, and 78% had a written policy governing data access. Criteria for the study approval and granting data access are up to the data controller (legal person, public authority or agency) and vary between organisations. In most EU countries, prospective studies should undergo Ethics Committee (EC) review prior to conduct, whereas retrospective do not have to; it is, however, often recommended to inform EC of conduct of such studies. Pseudonymisation, which implies that data identifying a person directly are replaced by a clear identifier, can be used to process patient personal data in a secure and confidential way. Obtaining approval from EC takes about 1–2 months, whereas it takes 3–4 months to obtain approval to access data.

Conclusions: Results provided insight on when and how the use of secondary data for health research requires approval by Ethics and data protection committees. These processes have considerable lead time, and heterogeneity in implementation of directive (95/46/EC) was noted.

331. The ADVANCE Code of Conduct: A Tool for Vaccine Benefit–Risk Monitoring in Europe

Xavier Kurz,[1] Vincent Bauchau,[2] Jorgen Bauwens,[3] Phillip Bryan,[4] Stephen Glismann,[2] Mirna Robert-Du Ry van Beest Holle,[5] Raphaele Roten,[6] Miriam Sturkenboom,[7] Lieke van der Aa,[8] Jane Whelan.[5] *[1]European Medicines Agency, London, UK; [2]GlaxoSmithKline, Brussels, Belgium; [3]Basel University, Basel, Switzerland; [4]MHRA, London, UK; [5]Novartis Pharma BV, Amsterdam, The Netherlands; [6]Crucell Holland BV, Leiden, The Netherlands; [7]Erasmus University, Rotterdam, The Netherlands; [8]WIV-ISP, Brussels, Belgium.*

Background: Experience with pandemic influenza vaccines in Europe highlighted weaknesses in data collection on vaccine exposure, safety, and effectiveness, including difficulties to set up efficient collaborations due to concerns about funding mechanisms and perception of conflicts of interest. The IMI project Accelerated Development of Vaccine benefit–risk Collaboration in Europe (ADVANCE) aims to establish a reliable, valid, and evaluated framework that could rapidly provide scientific evidence on vaccine benefits and risks. As part of this project, an agreed Code of Conduct (CoC) aims to facilitate public–private interactions while maintaining public trust.

Objectives: The aim of this study was to describe the components of the ADVANCE CoC to facilitate interactions between stakeholders for vaccine benefit–risk monitoring activities in Europe.

Methods: Core elements relevant to CoC were extracted from 16 national and international guidelines. A literature review identified the evidence base to support these core elements. Recommendations from guidelines were compiled and critically appraised by ADVANCE in order to achieve consensus on elements of a draft CoC. A broad public consultation of the draft CoC was initiated.

Results: Although a useful starting point, none of the reviewed guidelines fulfilled comprehensively the needs for vaccine studies taking into account different constraints, needs and requirements of stakeholders involved in vaccine studies. Ten key components of a CoC were identified: preparation and publication of the study protocol, research contract, management of potential conflicts of interest, scientific independence, confidentiality, transparency, ownership of results, access to data, study report, publications, and communications. Roles and responsibilities and minimum quality requirements are other key elements being developed. The applicability of the CoC to different stakeholders and the testing of its feasibility in proof-of-concept studies are described.

Conclusions: As part of the development of the ADVANCE framework, agreement of a specific CoC applicable to the complex environment of vaccine studies was deemed necessary. The draft CoC will be tested in upcoming proof of concept studies.

332. Assessment of Sex-specific Differences in Adverse Event Following Immunization Reporting in Ontario, Canada

Tara M Harris,[1] Kenny Wong,[1] Jill Fediurek,[1] Shelley L Deeks.[1,2] *[1]Immunization & Vaccine Preventable Diseases, Public Health Ontario, Toronto, ON, Canada; [2]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada.*

Background: Female predominance in adverse events following immunization (AEFI) reporting has consistently been observed in vaccine safety surveillance systems. While reasons are likely multi-factorial, growing evidence suggests that differences in sex-specific responses to vaccines may play an important role.

Objectives: The aim of this study was to describe AEFIs by sex with an emphasis on sex-specific trends by vaccine and reaction.

Methods: AEFIs reported in Ontario, Canada, following vaccines administered in 2012 and 2013 were extracted from the integrated Public Health Information System. Descriptive analyses were limited to "Confirmed" AEFIs with the female-only HPV program excluded. Events were grouped by provincial surveillance definitions. Reporting rates were calculated using provincial population estimates as the denominator. The World Health Organization definition of serious AEFI was used.

Results: There were 1219 AEFI reports following vaccines administered in 2012–2013. The annualized reporting rate was 4.5 per 100 000 population (5.9 and 3.0 per 100 000 for females and males, respectively); 66.9% of reports were female. The age-specific rate ratio for females versus males was highest in adults 18–64 years (5.8) compared with ≥65 (1.9) and children <18 years (1.2). Sex distribution varied by vaccine with female proportions highest for Td (tetanus, diphtheria), zoster, rabies, influenza, and pneumococcal polysaccharide vaccines (range: 69.0–91.3%). Reactions with the highest proportions in females included anaphylaxis (87.1%), anesthesia/paresthesia (84.2%), and adenopathy/lymphadenopathy (80.0%). Serious AEFIs were 55.4% female ($n = 31$) with similar reporting rates for females and males (0.21 vs. 0.19 per 100 000 population, respectively). Self-reported AEFIs versus reports by health professionals were more likely to be female (81.2% and 67.4%, respectively).

Conclusions: Female predominance in AEFI reports is observed primarily in adults with disproportionate reporting among females concentrated within specific vaccines and reaction-types but not within serious reports. Further analysis is indicated to assess trends within specific vaccines and the impact of variations in vaccine uptake by sex.

333. The Assessment of Characteristics of Adverse Events Following Immunization in Japanese Adverse Drug Event Report Database and Vaccine Adverse Event Reporting System for Signal Detection

Makoto Miyazaki, Akihito Shito, Minoru Shimodera. *Pharmacovigilance & Risk Management Area, MSD.K.K., Tokyo, Japan.*

Background: Adverse events following immunization (AEFIs) with a vaccine licensed in Japan have been accumulated in Japanese Adverse Drug Event Report database (JADER), especially since 01 April 2013, when an AEFI specified in the Japan national immunization program was required to be reported. Any AEFIs with a vaccine licensed in USA have been accumulated in Vaccine Adverse Event Reporting System (VAERS). There has been no report that assessed characteristics of AEFIs in JADER and VAERS.

Objectives: The objectives of this study were to perform signal detection by using JADER and VAERS and to assess characteristics of AEFIs in the databases by using results of the signal detection.

Methods: AEFIs reported from 01 April 2013 to 31 March 2014 were retrieved from the following three databases: data of Japanese AEFI cases in JADER (JADER-VC), data of US AEFI cases in VAERS (VAERS-US), and data of AEFI cases outside USA in VAERS (VAERS-FR). For signal detection, reported MedDRA PTs of AEFIs were defined as signaled PTs when a lower limit of a 95% confidence interval of their reporting odd ratio was >1.

Results: The data of JADER-VC, VAERS-US, and VAERS-FR from 01 April 2013 to 31 March 2014 included 4106 AEFIs (1293 cases), 116 516 AEFIs (30 610 cases), and 42 882 AEFIs (6804 cases), respectively. A proportion of AEFIs by SOCs and an age distribution of AEFI cases differed among the three databases. Signaled PTs differed among the three databases. For influenza injected vaccines, only one PT was commonly detected as a signaled PT. The number of signaled PTs was 14 out of 141, 168 out of 2139, and 121 out of 1433, respectively. A rate of AEFIs per AEFI case differed, and a mean age of AEFI cases in JADER-VC was younger than in VAERS-US and VAERS-FR.

Conclusions: Differences in a regulatory environment between Japan and USA, such as reporting criteria of AEFI cases and a recommendation for vaccination might cause differences in reported PTs, resulting in differences in signaled PTs. As the number of AEFIs in JADER-VC was limited at this study, we should consider that further accumulation of AEFIs might change the result of signal detection.

334. Is the Case–Population Approach Useful for Vaccine Safety Surveillance?

Hélène Théophile,[1,2] Antoine Pariente,[1,2,3] Nicholas Moore,[1,2,3] Bernard Bégaud.[1,2,3] *[1]Service de Pharmacologie Médicale, Centre de Pharmacovigilance, CHU, Bordeaux, France; [2]INSERM U657, Bordeaux, France; [3]Université de Bordeaux, Bordeaux, France.*

Background: The occurrence of vaccine safety concerns can compromise a successful vaccination campaign; early safety monitoring of vaccines from pharmacovigilance and pharmacoepidemiology is thus of primary importance. However, pharmacovigilance that has great ability to detect such issues early is limited for the quantification of associations. The case–population approach (CPA) compares the degree of exposure in cases with that of their source population, estimated using drug sales data. By using aggregated data, it could be useful for both the early detection of safety signal and the initial quantification of associations.

Objectives: The aim of this study was to assess the validity of the CPA for vaccine safety surveillance.

Methods: We searched in MEDLINE for case–control studies (CCS) quantifying risks associated with vaccine and for which the CPA could be applied. Odds ratio (OR) provided by the CPA was compared with that of CCS.

Results: ORs given by the CPA and the CCS were, respectively, 9.1 (95%CI 6.8–12.1) and 9.2 (95%CI 5.3–16.2) for intussusception and rotavirus vaccine, 2.7 (1.8–3.9) and 0.8 (0.3–2.2) for Gardasil® vaccine and idiopathic thrombocytopenic purpura, 0.8 (0.5–1.1) and 0.6 (0.2–1.5) for Gardasil® vaccine and connective tissue disorders, 0.3 (0.2–0.4) and 0.3 (0.1–0.7) for Gardasil® vaccine and central demyelination, 1.7 (1.3–2.2) and 1.2 (0.5–2.9) for Gardasil® vaccine and type 1 diabetes, 11.4 (6.8–19.0) and 5.5 (2.5–12.0) for A/H1N1 vaccine and narcolepsy in France, 1.2 (0.4–3.7) and 1.5 (0.4–7.0) for A/H1N1 vaccine and narcolepsy in Quebec, 2.3 (1.9–2.6) and 2.8 (1.3–6.0) for A/H1N1 vaccine and Guillain–Barré syndrome (GBS) in Europe, 3.7 (1.4–9.7) and 2.5 (0.7–9.3) for A/H1N1 vaccine and GBS in the Netherlands, 3.3 (1.1–9.8) and 2.3 (0.5–11.7) for A/H1N1 vaccine and GBS in Sweden, 3.2 (1.1–9.0) and 1.3 (0.3–6.4) for A/H1N1 vaccine and GBS in UK, 5.9 (2.0–17.4) and 9.5 (1.7–53) for A/H1N1 vaccine and GBS in Denmark.

Conclusions: In most situations, CPA association estimates were consistent to CCS ones. The observed disagreement with A/H1N1 vaccine could be explained by different levels of vaccination coverage between control and general populations and provide valuable information to further develop CPA.

335. The Development of an In-house Signal Mining and Management Tool for GSK Vaccine Spontaneous Reports

Lionel Van Holle, Pascale Schrauben. *Vaccine Clinical Safety and Pharmacovigilance, GSK Vaccines, Wavre, Belgium.*

Background: Monitoring vaccine safety using spontaneous report data needs to be flexible to quickly adapt to situations like mass vaccinations or pandemics. It also needs to use signal detection methods that are specific to vaccine data to detect features like dose-specific signals, manufacturing-related issues, unexpected temporal associations, disproportionate reporting, or clusters.

Objectives: The aim of this study was to develop a system that permits flexibility and allows users to "mine" the signals.

Methods: We developed a system composed of three independent compartments to maximize flexibility: data extraction from Argus, complementary signal detection algorithms developed in SAS, and standardized dynamic visualizations linking signals to the original data in Spotfire to allow data mining.

Results: The data extraction can be controlled to easily adapt how often signal detection is performed, for example, when an increased frequency is needed in pandemic situations. The set of signal detection algorithms can also be adapted to fine tune the methods to the specificities of the GSK vaccine spontaneous report database. Indeed, in addition to the regular disproportionality algorithm, it proposes an algorithm screening the reported time to onset for unexpected patterns and an algorithm integrating both quantified causality criteria of strength of association and temporality to predict the probability of an event being causally associated with a vaccine. The dynamic visualizations allow the end user to test specific hypotheses such as differences between demographic groups, doses, or clusters.

Conclusions: The flexibility offered by this system allows optimal use of spontaneously reported data to monitor patient safety. The compartmental approach will allow easy integration of safety data from other sources (vaccine dictionary and manufacturing data), new quantitative methods, or visualizations.

336. Screening Vaccine Spontaneous Reports Linked with Hierarchical Manufacturing Data: A Proof-of-concept of Manufacturing Safety Signal Detection

Olivia J Mahaux, Lionel F Van Holle. *Vaccines Clinical Safety and Pharmacovigilance, GlaxoSimth Kline, Wavre, Belgium.*

Background: Vaccines are produced through successive complex manufacturing steps that involve a large variety of ingredient lots. Some unexpected incidents at one of these steps could theoretically stay unnoticed by routine quality monitoring but could impact the quality of final vaccine doses and potentially jeopardize vaccinees' safety. It is important to be able to swiftly identify the potential production step most likely associated with safety problems to take urgent corrective measures.

Objectives: The aim of this study was to adapt the tree-based scan statistic (TBSS) to a screening method that identifies the production steps most likely associated with an excess in the spontaneous reporting of a particular adverse event (AE).

Methods: The successive manufacturing steps consist of raw material ingredient lots transformed into several intermediate ingredient lots until the final vaccine lots are produced. These manufacturing transformation relationships were used to create a hierarchical tree structure with the raw materials at one end and the final vaccines at the other end. The final vaccine lots administered to individuals are available in 34% of GSK spontaneous report data and constitute the link between manufacturing and safety data. The TBSS screened two simulated versions of these linked data: a version where the AE of interest was randomly redistributed among final reported lots and another version where excess of reports with the AE of interest was artificially controlled.

Results: The TBSS generated an expected number of false positive signals when applied to 100 randomized versions of the linked spontaneous data, demonstrating that it adjusted for multiple testing. The TBSS detected 73% of the simulated signals at the right production step when a fivefold increase in reports with the AE of interest was applied.

Conclusions: The hierarchical structure constructed from manufacturing data, which are linked with spontaneous report data by using reported lot information, is eligible for tree-based scan screening to detect the most likely production steps associated with an excess of AEs of interest.

337. The Incidence of Childhood and Adolescent Seizures in the UK from 1999 to 2011: A Retrospective Cohort Study Using the Clinical Practice Research Datalink

Cormac J Sammon,[1] Rachel A Charlton,[1] Julia Snowball,[1] John G Weil.[2] [1]*Department of Pharmacy and Pharmacology, University of Bath, Bath, UK;* [2]*Epidemiology Group, Novartis Vaccines and Diagnostics, Amsterdam, The Netherlands.*

Background: In postmarketing vaccine surveillance, adverse events observed in a vaccinated population are compared with the number expected based on a background incidence rate. The background rate should be accurate and obtained from a population

comparable with the one vaccinated. Such rates are often not available.

Objectives: The objectives of this study were to investigate the incidence of generalised convulsive seizure (GCS) in infants, children and adolescents in the UK Clinical Practice Research Datalink (CPRD) and determine to what extent CPRD data can be used to distinguish febrile from afebrile seizures.

Methods: GCS events were identified in individuals born after 01 January 1998 and aged between 2 months and 15 years using the CPRD (1999–2011). GCS events were categorised as febrile or afebrile using Read codes and free text, and the incidence of GCS, febrile seizures and afebrile seizures was calculated by age and calendar year.

Results: The study population consisted of 1 532 992 individuals (4 917 369 person years (PY) of follow-up). A total of 28 917 generalised convulsive seizure events were identified during follow-up; the overall incidence rate was 5.88 per 1000 PY. Age specific rates increased sharply from 4/1000 PY at 2 months of age, peaked at 19/1000 PY at 16 months and decreased until approximately 6 years of age at which point they became relatively stable at 2/1000 PY. Sixty-seven percent of GCSs were categorised as febrile: 56% using Read codes and 11% using free text. Febrile seizures accounted for the age trend in GCS, with rates peaking at 16.1/1000 PY at 16 months of age, while afebrile seizure rates remained relatively stable across all ages (2–4 seizures per 1000 PY). Analysis by first occurrence of febrile seizure showed a similar pattern, comparable with published studies on the incidence of seizures in childhood.

Conclusions: The CPRD can be used to identify febrile seizures. The rates reported in this study could be used in the postmarketing surveillance of infant vaccines. However, given the variation across strata and the underascertainment of seizure events presenting to A&E, care must be taken when interpreting and using these rates.

338. Pharmacoepidemiology in the Vaccine Industry: GSK Vaccines' Example of a Multidisciplinary Response to the Changing Regulatory Environment

Catherine Cohet,[1] Corinne Willame,[2] François Haguinet,[1] Dominique Luyts,[1] Vincent Bauchau,[1] Germano LC Ferreira,[1] Dominique Rosillon,[1] Laurence Baril.[1]
[1]GlaxoSmithKline Vaccines, Wavre, Belgium; [2]Business & Decision Life Sciences (for GlaxoSmithKline Biologicals SA), Wavre, Belgium.

Background: In a rapidly evolving regulatory environment and with new vaccines approaching approval or undergoing variations, researchers in the vaccine industry are increasingly facing the challenges of combining technical and operational expertise in a matrix environment while striving for the highest ethical standards and scientific integrity in pharmacoepidemiological research.

Objectives: The aim of this study was to describe multidisciplinary efforts at a vaccine company to evaluate safety signals and assess vaccine benefit/risk in real-world data settings.

Methods: Interactions with multiple internal and external stakeholders will be described and appraised based on evidence and learnings from regulatory commitments for recent vaccine programmes (rotavirus, influenza, human papillomavirus, and malaria).

Results: The last decade at GSK has seen multiple models for streamlining pharmacoepidemiology activities through dozens of post-approval safety and effectiveness studies. Progress has been driven by fast-advancing methodology, increasing understanding of the strengths and limitations of large databases, and the complexity of vaccine post-approval plans. Cross-functional sustainable capacity has been fostered through sharing knowledge and ensuring consistency in methodological approaches and between epidemiology, observational database analytics, biostatistics, regulatory and safety teams for the successful design, conduct, and report of post-licensure studies. This effort has been conducted in parallel with a growing need for public–private partnerships and synergistic efforts between vaccine manufacturers

Conclusions: In a rapidly changing regulated environment, robust multidisciplinary pharmacoepidemiology capability is key to ensure timely and relevant evidence generation, state-of-the-art methods, and high scientific integrity. Different organizational models embed strengths and limitations; the cornerstone remains in identifying and linking multiple internal stakeholders to ensure an agile delivery to regulators. At GSK vaccines, a cross-functional approach has proven effective in addressing numerous regulatory and public health questions

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339. Landscape Analysis of Existing Models of Public–Private Interactions in a Public Health Environment: An ADVANCE Initiative

Laurence Torcel-Pagnon,[1] Tin Tin Myint Htar,[2] Lisen Arnheim Dahlström,[3] François Simondon,[4] Vincent Bauchau,[5] Xavier Kurz.[6] *[1]Sanofi Pasteur MSD, Lyon, France; [2]Pfizer, Paris, France; [3]Karolinska Institute, Stockholm, Sweden; [4]Institut de Recherche pour le Développement, Marseille, France; [5]GlaxoSmithKline, Brussels, Belgium; [6]European Medicines Agency, London, UK.*

Background: Accelerated Development of Vaccine benefit–risk Collaboration in Europe (ADVANCE) is a public–private partnership supported by the Innovative Medicines Initiative. It aims to establish a framework rapidly providing reliable data on vaccine benefit–risk (B/R) for decision making. One of the objectives is to optimize innovative public–private synergies.

Objectives: A landscape analysis was performed to screen the existing public–private collaborations and partnerships in public health and to analyze them for further recommendations in governance models facilitating vaccine B/R monitoring in Europe.

Methods: A survey was conducted within ADVANCE partners (186 members from 47 organizations) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP] (137 centers) to collect information about multi-stakeholder interactions in public health and assess their strengths and weaknesses. A literature search was performed in PubMed to capture additional partnership models related to vaccine B/R studies. This analysis is based on the survey and literature review.

Results: Information on 70 different collaborations and partnerships were collected, 40 from the survey and 30 from the literature. Thirty-eight (54.3%) were between private–public, and 32 (45.7%) were between public–public partners. The roles of funder, responsible party, and data provider were taken up by single or multiples partners. A third party was involved in 61% of interactions; in most cases it was set up to endorse a neutral role between private–public partners or a coordination role between multi-partners. "Collaborative spirit," "knowledge and scientific expertise," and "improving public health" were the most cited strengths. Legal and funding challenges were commonly reported as areas of improvement.

Conclusions: Such a landscape analysis was never carried out before. Understanding the current status of public and private interactions and learning from previous experience will lead to recommend governance models for future synergies for vaccine B/R monitoring in Europe. This presentation is made on behalf of the members of ADVANCE WP1-WG3.

340. Safety and Tolerability Evaluation of the Use of Montanide ISATM 51 as Vaccine Adjuvant: A Systematic Review

Eva van Doorn,[1] Heng Liu,[1] Anke Huckriede,[2] Eelko Hak.[1] *[1]Pharmacy, University of Groningen, Groningen, The Netherlands; [2]Medical Microbiology, University of Groningen, University Medical Center of Groningen, Groningen, The Netherlands.*

Background: Montanide ISA 51 has been tested in thousands of subjects in therapeutic vaccine trials (e.g. cancer and HIV) and, recently, in a number of influenza vaccine trials. The inclusion of an adjuvant should be justified by a favorable risk/benefit ratio, the risk including adverse events (AEs).

Objectives: To our knowledge, this is the first systemic review on the assessment of the safety and tolerability of ISA 51.

Methods: A systematic literature search was conducted in PubMed, EMBASE, and clinicaltrials.gov for trials using ISA-51 adjuvanted vaccines. Trials reporting safety, tolerability, and/or toxicity data were categorized into (A) uncontrolled studies with non-healthy subjects, (B) controlled studies with non-healthy subjects, and (C) controlled studies with healthy subjects. Random effects meta-analyses were performed on studies including an active control group. The quality of the analyzed studies was assessed by Jadad score.

Results: We found 91 studies suitable for inclusion in our review; six of these including an active control group were eligible for meta-analyses. Generally observed AEs related to ISA 51-adjuvanted vaccines include injection site reaction and pain, myalgia, headache, GI disorders, fatigue, and fever, regardless of the administration route and subject characteristics. Serious AEs were reported in 27% of uncontrolled trials, and two trials conducted with healthy subjects were stopped because of unacceptable AEs in the ISA 51-adjuvanted vaccine group. None of the subjects in the adjuvant control group reported these AEs. Based on the meta-analyses, the reported

mainly mild-to-moderate AEs showed no statistically significant association with the use of ISA 51.

Conclusions: No specific safety and tolerability concern was identified for ISA 51 based on the meta-analyses. For trials including ISA 51, mixing with syringe is recommended to obtain stable emulsions and prevent AEs. In addition, future trials including adjuvanted vaccines need an active control group for a fair evaluation of adjuvant safety and tolerability. Furthermore, it is recommended that vaccine-related AEs be classified and reported according to a standardized reporting system.

341. Assessing Bias in Administrative Database Studies of Vaccine Completion Due to Exclusion of Subjects with Incomplete Follow-up

Scott C Quinlan,[1] T Christopher Mast,[2] Sander Greenland,[3] Crystal N Holick,[1] Stephan Lanes.[1] *[1]Safety and Epidemiology, HealthCore, Inc., Wilmington, DE, USA; [2]Epidemiology, Merck Research Laboratories, New Wales, PA, USA; [3]Epidemiology, UCLA School of Public Health, Los Angeles, CA, USA.*

Background: RotaTeq® pentavalent human rotavirus vaccine (RV5) is effective when administered as directed in the 3-dose schedule at ages 2, 4, and 6 months. Two studies have used automated claims databases to estimate the proportion of RV5-vaccinated infants who completed the dosing schedule but excluded from the analysis the vaccinated infants who were not enrolled in the database for a sufficient period to observe all 3 doses.

Objectives: The aim of this study was to determine if exclusions due to incomplete enrollment may have biased RV5 vaccine completion rates.

Methods: We conducted a claims database analysis in the HealthCore Integrated Research Database^{SM} (HIRD) to evaluate the proportion of RV5-vaccinated infants who completed the RV5 3 dose series using two methods. In the first analysis, we required continuous enrollment in the database from birth through first birthday. In the second analysis, we identified infants receiving the first dose who were enrolled in the database by 6 weeks of age and allowed for incomplete follow-up due to disenrollment.

Results: Requiring continuous enrollment for the first year of life resulted in only 40% of vaccinated infants being included in the analysis of completion rates. Relaxing inclusion criteria allowed 86% of vaccinated infants to be included. The estimated completion rates were 78.1% (95% confidence limits [CLs] 77.8%, 78.3%) among infants with continuous enrollment from birth through the first year of life, and 77.4% (95% CLs 77.2%, 77.6%) among the expanded population.

Conclusions: Excluding infants with incomplete follow-up in the database had a negligible impact on estimates of RV5 completion rates for this commercially insured population. Nonetheless, to increase the size of study populations and reduce the potential for bias, it is preferable to include subjects with incomplete follow-up in automated database analyses and adopt more robust approaches in defining and analyzing study populations that account for missing data.

342. Tumor Subtypes among Breast Cancer Patients with Diabetes

Heleen K Bronsveld,[1] Vibeke Jensen,[2] Pernille Vahl,[2] Marieke L de Bruin,[3] Sten Cornelissen,[1] Joyce Sanders,[4] Peter Vestergaard,[5] Marjanka K Schmidt.[1] *[1]Division of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2]Department of Pathology, Aarhus University Hospital THG, Aarhus, Denmark; [3]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands; [4]Division of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [5]Departments of Clinical Medicine and Endocrinology, Aalborg University, Aalborg, Denmark.*

Background: Diabetes mellitus (DM) and insulin treatment have been associated with increased breast cancer (BC) risk. Insulin treatment might be associated with the development of specific BC subtypes and subsequent differential survival.

Objectives: The aim of this study was to investigate whether diabetic patients, across categories of insulin analogue treatment, develop specific BC subtypes compared with non-diabetics.

Methods: This retrospective case–case study randomly recruited BC patients through the Danish Breast Cancer Cooperative Group in 2000–2010, stratified on age at BC diagnosis. Diabetic and non-diabetic BC patients were 2:1 matched on year of birth and 10-year age of

BC diagnosis categories, in order to select 300 patients. Formalin-fixed, paraffin-embedded tumor blocks were retrieved to construct tissue micro arrays (TMA), which were stained for ER, PR, HER2, Ki67, CK5/6, CK14, and p63. A pathologist scored all TMAs and revised tumor histological type and grade. BC subtypes among diabetic women treated with and without insulin analogues will be compared with BC without DM using multivariate logistic regression.

Results: 43 701 women diagnosed with primary incident BC were identified, of whom 3047 had DM (7.0%). For the analyses, 235 diabetic BC patients were selected and matched with 111 BC patients without DM, of which 227 and 103 had availability of tumor tissue, respectively. Patients with DM presented more breast tumors with grade 3 compared with non-DM patients (44.2% vs. 30.7%; $p = 0.043$), while no significant differences were observed between tumor size and number of positive lymph nodes. Preliminary analysis indicated that the percentage of patients with ER-negative (23.9% vs. 14.1%) or PR-negative tumors (35.5% vs. 24.5%) tended to be higher in the diabetic group. In addition, a higher percentage of diabetics compared with non-diabetics had positive staining for basal markers: CK5/6 (14.9% vs. 6.1%), CK14 (8.0% vs. 3.1%), and P63 (3.7% vs. 1.0%).

Conclusions: Based on these findings, there is an indication that DM patients tend to develop breast tumors that do not express hormonal receptors, which are typically associated with poor prognosis. This has implications when studying the associations between insulin treatment and BC.

343. Preliminary Results on the Impact of Genetic Factors on Gastrointestinal Bleeding in a Prospective Cohort of New Warfarin Users

Stephanie Dumas,[1] Sylvie Perreault,[1] Robert Côté,[2] Payman Shahabi,[3] Ian Mongrain,[3] Marie-Josée Gaulin,[3] Sylvie Provost,[3] Jean-Claude Tardif,[3] Marie-Pierre Dubé.[3] *[1]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada; [2]Department of Neurology and Neurosurgery, McGill University, Montreal, QC, Canada; [3]Beaulieu-Saucier Université de Montréal Pharmacogenomics Centre, Montreal Heart Institute, Montreal, QC, Canada.*

Background: Warfarin, a commonly prescribed oral anticoagulant, is well known for its narrow therapeutic index. Warfarin causes a third of emergency hospitalization due to adverse events in the elderly. Most of these complications are major gastrointestinal (GI) bleeds.

Objectives: Our goals were to investigate the potential risk factors of warfarin-related minor and major GI bleeding events and to examine their potential differential impact according to patient's genetic profile.

Methods: This study was based on a prospective cohort of new warfarin users; the objectives were to assess the genetic, clinical, and environmental risks associated with the effectiveness and safety of warfarin. Data were collected on 1069 patients who began the treatment between 1 May 2010 and 31 July 2013. Patients were followed up each 3 months for a year. The primary outcomes were the occurrence of a first minor or major GI bleed. We used a Cox regression analysis.

Results: Mean age was 70.8, 61.8% of patients were men, 68.4% had a history of hypertension and 60.8% of dyslipidemia, and 76.4% had atrial fibrillation as a primary indication for warfarin. Overall, 4.8% of patients reported ≥1 minor GI bleed, and 1.6% reported ≥1 major GI bleed. Patients with ≥1 polymorphism on both the CYP2C9 and the VKORC1 were significantly more at risk of having a major GI bleed (HR 10.72; $p = 0.023$). Patients with a history of MI or angina were at risk of having both minor and major GI bleeds (HR = 1.73 and HR = 2.63; $p < 0.05$). The impact of MI and angina disappeared for patients with no SNP on the CYP2C9 gene but was higher for patients with ≥1 SNP (HR = 2.44 and HR = 5.26, $p < 0.05$).

Conclusions: Our preliminary results suggest an interaction between MI or angina history and the occurrence of major and minor GI bleeds, especially in patients with ≥1 polymorphism on the CYP2C9 gene. Further analysis including concomitant use would help clarify clinical guidelines for this population and underlie the potential benefit of genetic testing.

344. Decision Analysis Model for Genetic Testing Prior to Antidepressant Treatment

Jacob T Painter,[1] Bradley C Martin,[1] Chenghui Li,[1] Amit Bodhani,[1] Jeffrey M Pyne.[2] *[1]Pharmaceutical Evaluation & Policy, University of Arkansas for Medical Sciences, Little Rock, AR, USA; [2]Psychiatry, University of Arkansas for Medical Sciences, Little Rock, AR, USA.*

Background: Depression is common and expensive in terms of disease burden and treatment costs in the United States. Efficacious antidepressant agents are available in multiple drug classes. Individual patient factors associated with depression are complex, and physicians often rely on "trial and error" when choosing a particular antidepressant medication. Genetic testing to determine metabolic genotypes provides an avenue to personalize pharmacotherapy decisions for depression.

Objectives: The objective of this paper is to estimate the cost-effectiveness of metabolic genetic testing, relative to no testing, using a decision analysis model. We will examine this model for patients beginning antidepressant treatment and for patients who have failed a previous antidepressant treatment trial.

Methods: We chose a model published by Sullivan *et al.* in 2004 to base our decision analysis. The order of the model was assignment to specific SRI, treatment response, ADR, response to ADR, and outcomes. We created a stochastic decision analysis model that replicated and validated the original Sullivan model using Tree Age Pro. The following adaptations were then made to the original Sullivan model. (i) Initial node was genetic testing for CYP2D6 polymorphisms. (ii) Experience of ADRs was moved ahead of treatment response. (iii) Three treatment strategies were modeled: (1) paroxetine initiation, (2) citalopram initiation, and (3) genetic test. The model used a 6-month time horizon to incorporate all costs and utilities. Model inputs were obtained from published sources and clinical assumptions.

Results: The base-case results demonstrate that both the gene chip arm and the paroxetine with no gene chip arm are more costly and less effective (dominated) compared with the citalopram with no gene chip arm. Therefore, in the base case, initiating treatment with citalopram is the preferred option over genetic testing.

Conclusions: Citalopram without the gene chip appears to be the dominant strategy, the explanation for this finding seems to be due to citalopram not being affected by CYP2D6 polymorphisms, having a comparable price with paroxetine and having lower ADR rates than paroxetine.

345. Association between Genetic Polymorphisms of Drug-metabolizing Enzymes and Transporters and Anti-tuberculosis Drug-induced Liver Injury in a Chinese Population

Ru Chen,[1] Jing Wang,[1] Shaowen Tang,[2] Yuan Zhang,[3] Xiaozhen Lv,[4] Siyan Zhan.[1] *[1]Department of Epidemiology and Biostatistics, Peking University Health Science Centre, Beijing, China; [2]Department of Epidemiology and Biostatistics, Nanjing Medical University, Nanjing, China; [3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; [4]Clinical Research Division, Peking University Institute of Mental Health, Beijing, China.*

Background: Anti-tuberculosis drug-induced hepatotoxicity (ATDH) is one of the leading adverse drug reactions during the course of tuberculosis treatment. Evidence indicates that the polymorphisms in genes encoding drug-metabolizing enzymes and transporters may play an important role in the development of ATDH.

Objectives: The aim of this study was to investigate the association between genetic polymorphisms of drug-metabolizing enzymes and transporters and the risk of ATDH in a Chinese cohort.

Methods: The study was designed as a nested case–control study within a prospective cohort. Each ATDH case was matched with four controls on the basis of age, gender, treatment history, disease severity, and drug dosage. The single-nucleotide polymorphisms (SNPs) were selected using Haploview 4.2 based on the Hap-Map database of Han Chinese in Beijing and genotyped by TaqMan allelic discrimination technology. We applied classic tests to assess individual SNP associations and the least absolute shrinkage and selection operator (LASSO)-penalized logistic regression analysis to assess multiple SNPs simultaneously. Odds ratio (OR) with 95% confidence intervals (CIs) was estimated by conditional logistic regression model with adjusting the body weight and usage of liver protective drugs.

Results: A total of 89 incident ATDH cases and 356 controls undergoing anti-tuberculosis treatment were included. Fifty-one SNPs in 23 genes encoding drug-metabolizing enzymes and transporters were selected for genotyping. Based on classical analyses, significant differences were found in SNPs of SLCO1B1, CYP7A1, and ABCG2 at p-value ≤ 0.05. LASSO regression selected rs4149014 in SLCO1B1 and rs2231137 in ABCG2. After correction for potential confounding factors, the ORs under the recessive model were 0.14 (95%CI, 0.03–0.60; $p = 0.008$) and 0.23 (95%CI, 0.07–0.80; $p = 0.02$) for rs4149014 and rs2231137, respectively.

Conclusions: Our study suggests that genetic variants in drug transporters such as SLCO1B1 and ABCG2 are associated with the development of ATDH in Chinese population. Additional studies in larger, varied populations are required to confirm these findings.

346. Prevalence and Characteristics of Non-small Cell Lung Cancer (NSCLC) Patients Harboring Oncogenic Drivers

Dixa B Thakrar,[1] Ceri Hirst.[2] *[1]School of Medicine, University of Leicester, Leicester, UK; [2]Biometrics, Roche, Basel, Switzerland.*

Background: With 1.8 million annual cases, lung cancer is the most commonly diagnosed cancer in the world but has a poor prognosis. NSCLC is known to harbor oncogenic drivers, which play a role in progression and sustenance of disease. Targeted therapy may improve outlook for these patients (pts), but the epidemiology of some of these biomarkers is not yet well understood.

Objectives: The aim of this study was to determine prevalence and characteristics of NSCLC pts with oncogenic drivers.

Methods: To identify studies on prevalence and characteristics of NSCLC pts with oncogenic drivers, a systemic review of studies published since 2009 was conducted using MEDLINE and handsearching reference lists. Biomarkers included EGFR, KRAS, ALK, BRAF, PIK3CA, HER2, RET, and PD-L1. Studies with ≥90 subjects were included.

Results: Approximately 90 studies were yielded. In unselected NSCLC populations tested for the oncogenic drivers of interest, we found the following. Prevalence of EGFR mutation was higher in Asian (~35%) than European (~13%) and North American (~18%) pts. KRAS mutation occurred more among European and North American (~25–28%) than Asian pts (~10%). ALK fusions occurred in ~2–6% of the Asian NSCLC population and ~4–7% of North American populations. Prevalence of other markers were similar between Asian and North American NSCLC pts: BRAF (1% vs 2%); HER2 (2% vs 3%); PIK3CA (2% vs 3%). RET fusions occurred in 1–2% of Asians. PD-L1 overexpression was ~50% across all populations. Male gender and smoking status/history were more associated with KRAS or PIK3CA mutations and less with EGFR mutation, ALK, or RET fusions. Variability of estimates between studies was noted and partly explained by test methods, undisclosed/unintentional pt selection, and heterogeneous populations.

Conclusions: While a high degree of variability was noted between estimates in different studies, the review highlights the differences in prevalence across Asian, European, and North American populations and the distinction in the characteristics among pts with these oncogenic drivers. This heightened understanding may help clinicians decide what genetic tests are suitable for pts and aid development and distribution of targeted therapies.

347. A National Survey of Pharmacists' Roles in Clinical Pharmacogenomics: Assessment of Predictors

Emily Schwartz,[1] Amalia M Issa.[1,2] *[1]Philadelphia College of Pharmacy & Program in Personalized Medicine & Targeted Therapeutics, University of the Sciences in Philadelphia, Philadelphia, PA, USA; [2]Program in Personalized Medicine & Targeted Therapeutics and Dept of Health Policy & Public Health, University of the Sciences in Philadelphia, Philadelphia, PA, USA.*

Background: As pharmacogenomics (PGx) becomes increasingly integrated into clinical practice, pharmacists will need to become more involved in decisions related to PGx testing and its influence on medication management. However, little is known about the role of pharmacists in the future delivery of PGx and the potential impact on adverse drug reactions (ADRs) and drug utilization.

Objectives: The objectives of this study were to assess knowledge, attitudes, and educational needs of hospital pharmacists about clinical PGx and to evaluate predictors of adopting PGx approaches by pharmacists.

Methods: A national panel of hospital pharmacists were surveyed using a secure Qualtrics web-administered 25-question survey. Linear regression models of predictor variables for pharmacist adoption and use of PGx were analyzed. Data were analyzed using SPSS.

Results: The survey was administered to 660 pharmacists, and there was a 23% response rate ($n = 149$). The majority of surveyed pharmacists (72%) reported that they are aware of the importance of PGx in clinical

practice, and of its benefit for patient care, and are in favor of implementing it. However, only 25% of pharmacists are confident in their ability to interpret PGx test results. Seventy-nine per cent of pharmacists reported being concerned that insurance companies may have a negative influence on pharmacogenomics. Thirty-four per cent reported concern that testing results may suggest that there is no available beneficial pharmacotherapy for their patients. Of the predictor variables tested, "confidence" was the most strongly associated with intent to adopt and use PGx ($p < 0.01$). Eighty-five per cent of pharmacists would prefer online self-training, and 39% would prefer training at a national meeting to meet PGx learning needs.

Conclusions: Pharmacists are critical to the implementation of PGx in clinical practice; however, they demonstrate gaps in knowledge and confidence in their abilities to interpret and use PGx information in clinical care. This has implications for ADRs and drug utilization, and future studies should be conducted to assess utilization and practice patterns of pharmacists relevant to PGx and outcomes of using PGx in practice.

348. Observational Medical Outcomes Partnership (OMOP) and Mini-Sentinel (MS) Common Data Models and Analytics: A Systematic Data Driven Comparison

Xiaofeng Zhou,[1] Xu Yihua,[2] Brandon T Suehs,[2] Abraham G Hartzema,[3] Michael G Kahn,[4] Yola Moride,[5] Brian Sauer,[6] Qing Liu,[1] Keran Moll,[2] Margaret Pasquale,[2] Vinit Nair,[2] Andrew Bate.[1] *[1]Pfizer Inc, New York, NY, USA; [2]Humana Inc, Louisville, KY, USA; [3]College of Pharmacy, University of Florida, Gainesville, FL, USA; [4]Department of Pediatrics, University of Colorado, CO, USA; [5]Faculty of Pharmacy, Université de Montreal, Montreal, QC, Canada; [6]University of Utah, UT, USA.*

Background: A key component to coordinating surveillance activities across distributed networks is the design and implementation of a common data model (CDM). There is a lack of literature on systematic comparison of OMOP and MS CDMs and analytics.

Objectives: The aim of this study was to evaluate two drug safety surveillance ecosystems to better understand how differences in CDMs and analytic tools affect usability and interpretation of results.

Methods: Humana claims data from 2007 to 2012 were mapped to OMOP and CDMs. Data were described and compared at the patient-level, by source code and mapped concepts. Study construction and effect estimates were also compared using two different analytical methods—high dimensional propensity score (HDPS) and univariate self-controlled case series (USCCS)—across six drug–outcome pairs considered that established positive associations to learn how differences in CDMs and analytics influence steps in the database analytic process and results.

Results: Data for a total of 7.5 million patients in Humana claims data were transformed into OMOP and MS CDMs. The differences in the design and structure of CDMs, the cohort identifications, and the method performance were identified. Three health outcomes of interest and two drugs of interest showed differences in cohort size and constituency between two CDMs. Overall, MS HDPS on MS CDM detected more known positive associations (performance score: 50–67%) compared with OMOP HDPS on OMOP CDM (performance score: 17–50%). The USCCS method results were comparable (performance score: 67–67% on MS CDM vs. 67–83% on OMOP CDM). Selection of analytic model and risk period specification had a significant impact on the performance of the OMOP HDPS method.

Conclusions: Differences observed between the OMOP and MS CDM ecosystems could be attributed to CDM structure, CDM mapping, analytic procedures, and intended purpose of use. Our results suggest that such differences at the ecosystem level of analyses can lead to striking differences in identifying a known safety signal. However, many differences between CDMs could be avoided with thoughtful and informed use of the data.

349. Criteria to Choose Linkage Methods: A Simulation Study

Ying Zhu,[1] Yutaka Matsuyama,[1] Yasuo Ohashi,[1] Soko Setoguchi.[2] *[1]The University of Tokyo, Tokyo, Japan; [2]Duke Clinical Research Institute, Durham, NC, USA.*

Background: When unique identifiers are not available, successful record linkage depends greatly on data quality and availability. While probabilistic linkage (plink) theoretically captures more true matches than deterministic linkage (dlink) by allowing

imperfection in identifiers, studies have shown inconclusive results.

Objectives: The simulation study aimed to understand data characteristics that affect the performance of plink versus dlink and to make practical recommendations to choosing linkage methods.

Methods: We created 96 scenarios that represent real-life situations using five non-unique identifiers. We introduced a range of (1) discriminative power, (2) rate of missing and error (≤2.5% to ≤20%), and (3) file size of equal ratio (1000; 10 000; 50 000) and unequal ratio (1:1; 1:5; 1:20) to increase linkage patterns and difficulties. An error-free unique identifier was introduced as the gold standard. We assessed performance difference of dlink and plink using validity measures and computation time.

Results: False positive (FP) link rate of plink and false negative (FN) link rate of dlink, limiting factor of the respective method, were mainly affected by rate of missing and error entries. Plink uniformly outperformed dlink. However, with very high-quality data (<3% error), dlink performed not significantly worse—both methods generated >95% sensitivity and >95% positive predictive value (PPV). Equal or more matches were identified by plink than dlink when discriminative power and error entries increased independently or simultaneously. Increase in file size inflated FP and decreased PPV of both methods, and it increased the computation time of plink from 2 minutes to 2 hours, while dlink always took <1 minute in SAS.

Conclusions: Choosing linkage method is a case-by-case decision. One must consider database quality, uniqueness of identifiers, file size, project-specific penalties associated with FP and FN links, familiarity with matching procedure and database, linkage software, and computation time. In general, plink is a better choice, but for exceptionally good-quality data (<3% error), dlink is more resource efficient. More research is needed to create general guidelines applicable to different linkage scenarios.

350. Lessons Learned in Replicating FDA's Sentinel Modular Programs

Hoa V Le,[1] Charlotte Carroll,[1] John Logie,[2] Carlyne Averell,[1] Chi TL Truong,[1] Jennifer B Christian.[3] *[1]Worldwide Epidemiology, GlaxoSmithKline, RTP, NC, USA; [2]Worldwide Epidemiology, GlaxoSmithKline, Stockley Park, Middlesex, UK; [3]Clinical Effectiveness & Safety, GlaxoSmithKline, RTP, NC, USA.*

Background: FDA has built a national rapid-response electronic safety surveillance system, the Sentinel System, to enable rapid assessments of drugs and other regulated medical products.

Objectives: The aim of this study was to implement and compare Sentinel's key modular programs (MPs) on commercially available US healthcare claims databases.

Methods: Analyses of dabigatran, warfarin, intracerebral hemorrhage (ICH), and gastrointestinal hemorrhage were conducted in four US healthcare claims databases, replicating results already in the public domain. Modules were parameterized based on protocol information provided on the Sentinel website. MPs were enhanced by adding confidence intervals (CI) and age-standardized incidence rates (IR) per US Census 2010 to facilitate comparisons with summary estimates from the Sentinel distributed network.

Results: MPs 1 and 4 were implemented to provide descriptive exposure information (e.g., number of incident/prevalent users, person-time exposed, number of days supplied, and concomitant medication use). MP3 was used to estimate crude IR stratified by gender and age. Figures varied across databases for each exposure–outcome pair under study relative to the overall Sentinel summary statistics. For example, among individuals with a pre-existing atrial fibrillation in 2010 and 2011, the IR of ICH per 100 000 person-day at risk for dabigatran users varied from 0.36 to 0.77 relative to the Sentinel summary statistic of 0.61. After age-standardization, adjusted results were 0.08–0.23 (95%CI: 0.03–0.34) relative to an age-standardized Sentinel summary estimate of 0.11 (95%CI: 0.02–0.21).

Conclusions: It was important to understand the methodological approaches used within FDA's Sentinel MPs and to demonstrate the feasibility of replicating both the methods and the results within other US data sources. Although results varied across data sources for each exposure–outcome pair under study, many findings were similar to the Sentinel summary estimates after using the proposed enhancements.

351. Transparency and Reproducibility of Published Analyses of Cohort Studies in Healthcare Databases

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Shirley V Wang,[1] Patrice Verpillat,[2] Jeremy A Rassen,[3] Dorothee B Bartels.[2] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical/Brigham & Women's Hospital, Boston, MA, USA; [2]Boehringer Ingelheim, Ingelheim, Germany; [3]Aetion, Inc, New York, NY, USA.*

Background: The scientific community and decision makers are increasingly concerned about transparency and reproducibility of epidemiologic studies using longitudinal healthcare databases (DBs).

Objectives: The aim of this study was to evaluate the extent to which published pharmacoepidemiologic studies using commercially available electronic medical records and claims DBs can be reproduced by other investigators.

Methods: We identified a non-systematic sample of >100 studies published between 2008 and 2014 using CPRD, MarketScan, or UnitedHealth. These studies evaluated safety or effectiveness of drugs or described characteristics of enrolled populations. Studies lacking sufficient detail on inclusion/exclusion criteria, follow-up time, or covariate/outcome identification were excluded. We used the Aetion evidence platform to expedite reproduction of the remaining studies. The Aetion platform was validated against pre-programmed and tested software macros in routine use by the FDA's Sentinel Program or via double programming. Metrics for reproducibility included population size, population characteristics, and size of adjusted effect estimates.

Results: Nearly 50 studies were excluded because critical parameters for reproducing the work were not reported. Another 20 published studies were excluded as they were operationalized in a way that violated basic design and analysis principles, including immortal time bias, adjustment for causal intermediates, and inconsistent temporality. In 34 studies published with sufficient detail on study implementation, we were able to reproduce 1031 dichotomous patient characteristics (median difference 0.0%) and effect estimates with a high degree of accuracy (all within CI overlap).

Conclusions: A critical step to transparent and reproducible research with healthcare DBs is a more complete reporting of study implementation. With the availability of electronic appendices in almost any scientific journal, word limits are not a barrier to detailed reporting of key operational decisions, for example, including codes used for outcomes/covariate definition. It is concerning that up to 20% of the studies were implemented in a way that makes causal conclusions problematic.

352. Privacy-preserving Multivariate Analyses Using Propensity Scores When Patient Information Is Stored in Disparate Locations (Vertically Distributed Data)

Sebastian Schneeweiss, Justin Bohn, Wesley Eddings. *Division of Pharmacoepidemiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.*

Background: Distributed networks of healthcare data sources are being increasingly utilized to conduct pharmacoepidemiology database studies. Such networks may contain data that are not physically pooled but are instead distributed horizontally (separate patients within each data source) or vertically (separate features of the same patients within each data source), in order to preserve patient privacy. While multivariate methods for the analysis of horizontally distributed data are described and frequently employed (e.g., FDA Sentinel), few practical approaches have been put forth to deal with vertically distributed healthcare databases.

Objectives: We propose two novel propensity score (PS)-based approaches to vertically distributed multivariate data analysis and test their performance using five example studies.

Methods: Existing propensity score PS-based methods for horizontally distributed data can be expanded to accommodate vertically distributed data by separately estimating PSs within distinct data domains (e.g., claims, lab tests, and genetic data) and then combining these PSs into a single PS. One can estimate the PS in each data domain separately (parallel), or one can estimate the PS in one domain first and then pass that PS on to the next data domain for inclusion in a second PS model, iteratively working through all available domains (sequential).

Results: In five example studies using various healthcare databases, we found point estimates with these approaches close to what could be achieved with no partitioning (mean squared error: 0.001 to 0.038), even in the presence of partially missing data in a single data domain (MSE: 0.0004 to 0.0379). We further found a performance benefit for sequentially passing a PS through each data domain (sequential approach)

over fitting separate domain-specific propensity scores (parallel approach).

Conclusions: This proof-of-concept study suggests a new multivariate analysis approach to vertically distributed healthcare databases that is practical and preserves patient privacy. The sequential approach performs slightly better, but the parallel approach is easier to implement in practice.

353. Assessing Assumptions of Instrumental Variables through Linkage To External Data

Gang Fang,[1] Izabela Annis,[1] M Alan Brookhart.[2] *[1]Division of Pharmaceutical Outcomes and Policy, UNC at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Epidemiology, UNC at Chapel Hill, Chapel Hill, NC, USA.*

Background: Instrumental variable (IV) analysis can control for measured and unmeasured confounding for comparative effectiveness research (CER). However, finding a valid IV is challenging. Linkage to external clinical data may help with IV validation.

Objectives: The aim of this study was to assess and compare four types of commonly used IVs (differential distance to healthcare provider, hospital market region, individual physician preference, and small area practice preference) through data linkage.

Methods: IVs were constructed using Medicare Chronic Condition Data Warehouse (CCW) claims for elderly patients with acute myocardial infarction (AMI) in 2008 in the USA. To assess the IVs' assumption of strong association with treatment (β blockers use), we primarily used the Wald denominator. To assess the IVs' assumption of natural experiment, we assessed prevalence difference ratio (PDR) of covariates balance measured from CCW claims (confounders between treatment and outcomes) and AMI core measures obtained from the linked University Health System Consortium's (UHC) Clinical Database (confounders between IV and outcomes). The effects of β blocker use on cardiovascular events were estimated.

Results: The strength of the four IVs constructed varied. The hospital market region-based instruments were the strongest in the full cohort and linked subgroup. The PDR among the IVs also varied with the small area practice preference-based instruments having smallest PDR in the full cohort and subgroup. The IVs had considerable differences in the estimates of β blocker effects.

Conclusions: Empirically constructed instruments had varied abilities in satisfying the assumptions as valid instrumental variables. Careful examination of multiple instruments and possible linkage to external clinical database for validation is important.

354. Association between Trajectories of Statin Adherence and Subsequent Cardiovascular Events

Jessica Franklin,[1] Alexis Krumme,[1] Angela Tong,[1] William Shrank,[2] Olga Matlin,[2] Troyen Brennan,[2] Niteesh Choudhry.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]CVS Caremark, Woonsocket, RI, USA.*

Background: Group-based trajectory models identify groups of patients with similar patterns of adherence and model adherence in each group over time. Medication adherence trajectories have been found to accurately summarize longitudinal adherence patterns and classify patients into clinically meaningful groups, but the association between adherence trajectories and clinical outcomes remains unclear.

Objectives: The aim of this study was to investigate the association between 12-month statin trajectories and subsequent cardiovascular events.

Methods: We identified patients who received insurance coverage from a large national insurer and initiated a statin during 1 January 2007 to 31 December 2010. We assessed medication adherence during the 360 days following initiation and grouped patients based on the proportion of days covered (PDC) during each 30-day period of adherence assessment using group-based trajectory models. We then measured cardiovascular events during the year after adherence assessment. Cox proportional hazards models were used to evaluate the association between adherence measures and cardiovascular outcomes; strength of association was quantified by the hazard ratio (HR), the increase in model C-statistic, and the net reclassification index (NRI).

Results: Among 519 842 statin initiators, 8777 (1.7%) had a cardiovascular event during follow-up. More

consistent medication use was associated with a lower likelihood of clinical events, whether adherence was measured through trajectory groups or PDC. When evaluating the prediction of future cardiovascular events by including a measure of adherence in the model, the best model reclassification was observed when adherence was measured using three or four trajectory groups (NRI = 0.189 [95% confidence interval: 0.171, 0.210]).

Conclusions: Statin adherence trajectory predicted future cardiovascular events better than measures categorizing PDC. Thus, adherence trajectories may be useful for targeting adherence interventions or adjusting for adherence behavior in comparative effectiveness studies.

355. The Effect of Adherence to Statin Therapy on the Hazard of Cardiovascular Mortality in the Netherlands

Maarten J Bijlsma,[1] Stijn Vansteelandt,[2] Fanny Janssen,[3] Hak Eelko.[1] *[1]Pharmacoepidemiology & Pharmacoeconomics, University of Groningen, Groningen, The Netherlands; [2]Department of Applied Mathematics, Computer Science and Statistics, University of Ghent, Ghent, Belgium; [3]Population Research Centre, University of Groningen, Groningen, The Netherlands.*

Background: The biological efficacy of statin therapy has been demonstrated in various clinical trials. However, end users may differ from trial participants in relevant ways. Therefore, observational studies are needed to assess clinical effectiveness. Our objective was to assess the clinical effectiveness of adherence to statin therapy in reducing cardiovascular mortality in the Netherlands.

Objectives: The aim of this study was to assess the clinical effectiveness of adherence to statin therapy in reducing cardiovascular mortality in the Netherlands.

Methods: Individual-level mortality information from Statistics Netherlands was linked to pharmacy dispensing data that came from the representative database IADB.nl. We used extended Cox models with adherence to statin therapy as the primary exposure and time to cardiovascular mortality as the primary outcome. We adjusted for age, sex, birth cohort, socio-economic status, diabetic status, and the utilization of various cardiovascular drugs. Covariates were allowed to vary over time. We achieved population-averaged effect estimates through implementation of the parametric G-formula. We also performed a subset analysis by calendar period corresponding to periods of particular cardiovascular prescribing guidelines and a subset analysis by dispensing background to assess the influence of healthy adherer bias.

Results: The conditional estimate was that being fully adherent to statins reduced the hazard of cardiovascular mortality by about 47% (HR: 0.53; 95%CI: 0.46 to 0.61), compared with being fully non-adherent to statins. The population-averaged estimate was of similar magnitude. In addition, we found evidence that estimates of clinical effect approached estimates of trials just after the introduction of statins in the population but became potentially more confounded in later calendar years.

Conclusions: The study provides evidence of the clinical effectiveness of statins, although the final estimates may still be affected by healthy adherer bias.

356. The Risk of Acute Myocardial Infarction after Discontinuation of Antihypertensive Agents

Fawaz F Alharbi, Patrick C Souverein, Mark CH de Groot, Anke H Maitland-van der Zee, Anthonius de Boer, Olaf H Klungel. *Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.*

Background: Sudden discontinuation of some antihypertensive agents such as beta-blockers and centrally acting antihypertensive agents are associated with increased risk of acute coronary events.

Objectives: The aim of this study was to assess the association between discontinuation of different antihypertensive agents and the risk of acute myocardial infarction (AMI).

Methods: A nested case control study was performed in a cohort of antihypertensive drug users from the Utrecht Cardiovascular Pharmacogenetics (UCP) database. Within this cohort, patients who were hospitalized for first AMI were considered cases. Cases were matched (1 up to 4) to controls at the same AMI date (index date). Antihypertensive users were defined as

current users if the index date fell within prescribed duration or as stoppers if this date fell outside the prescribed duration. According to recency of stopping, stoppers were divided into recent stoppers (≤90 days), intermediate-term stoppers (91–180 days), and long-term stoppers (>180 days). The study included only antihypertensive users who were specifically current users or stoppers of one antihypertensive agent. Logistic regression analysis was used to assess the association between the discontinuation of antihypertensive agents and the risk of AMI and to control for confounding.

Results: We included 1245 cases and 4994 controls in our analysis. The risk of AMI was significantly increased with all stoppers of beta-blockers (adjusted OR: 1.54, 95%CI (1.25–1.90)), calcium channel blockers (CCBs) (adjusted OR: 2.25, 95%CI (1.53–3.30)), and diuretics (adjusted OR: 1.76, 95%CI (1.24–2.48)) compared with current users. Moreover, the risk of AMI was significantly increased for long-term stoppers (beta-blockers, CCBs, angiotensin-converting enzyme inhibitors, and diuretics) and intermediate-term stoppers (beta-blockers and CCBs) versus current users. There was no difference in AMI risk between recent stoppers of antihypertensive agents versus current users.

Conclusions: Discontinuation of antihypertensive agents increases the risk of AMI after more than 90 days of stopping. Adherence to antihypertensive agents plays an important role in reducing the risk of AMI in patients with hypertension.

357. Use of Antihypertensive Agents and the Risk of Out-of-hospital Cardiac Arrest: A Case Control Study

Fawaz F Alharbi,[1] Patrick C Souverein,[1] Marieke T Blom,[2] Hanno L Tan,[2] Anthonius de Boer,[1] Olaf H Klungel.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.*

Background: Sudden cardiac arrest (SCA) is a complex multifactorial condition and is commonly caused by ventricular tachycardia/fibrillation (VT/VF). Some antihypertensive agents such as thiazides are associated with increased risk of SCA.

Objectives: The aim of this study was to assess the association between different antihypertensive agents and the occurrence of out-of-hospital cardiac arrest (OHCA), taking into account their potential impact on serum potassium levels.

Methods: Cases were drawn from the Amsterdam Resuscitation Studies (ARREST) registry and controls from the PHARMO database. This study was performed using 1948 cases who had OHCA with electrocardiogram (ECG)-documented VT/VF for the first time. These cases were matched by age, sex, and OHCA date (index date) to 8347 controls. From this dataset, we included only patients who were current users of antihypertensive agents (the index date fell between start date and end date of prescription + 10%). Antihypertensive therapies were classified according to their potential impact on serum potassium levels to therapies with neutral effect, therapies inducing hypokalemia, therapies inducing hyperkalemia, and therapies with unknown effect. Logistic regression analysis was used to study the association between use of antihypertensive agents and occurrence of OHCA and to control for confounding.

Results: We included 1192 cases and 3303 controls who were current users of antihypertensive agents in our analysis. The risk of OHCA was significantly increased with users of antihypertensive therapies inducing hypokalemia (adjusted OR 1.48, 95%CI (1.12–1.94)) and with users of antihypertensive therapies with unknown effect (adjusted OR 1.42, 95%CI (1.13–1.77)) versus users of antihypertensive therapies with neutral effect. There was no difference in OHCA risk between users of antihypertensive therapies inducing hyperkalemia versus users of antihypertensive therapies with neutral effect (adjusted OR 1.13, 95%CI (0.89–1.43)).

Conclusions: The risk of OHCA is significantly increased in patients who were current users of antihypertensive therapies inducing hypokalemia and antihypertensive therapies with unknown effect on serum potassium levels.

358. ABCB1 Gene Variants, Digoxin, and Risk of Sudden Cardiac Death in a General Population

Maartje N Niemeijer, Marten E van den Berg, Jaap W Deckers, Adrianus LHJ Aarnoudse, Albert Hofman, Oscar H Franco, Andre G Uitterlinden, Peter R

Rijnbeek, Mark Eijgelsheim, Bruno H Stricker. *Erasmus MC - University Medical Center Rotterdam, Rotterdam, The Netherlands.*

Background: The ATP-Binding Cassette B1 (ABCB1) gene encodes P-glycoprotein, a transport protein, which plays an important role in the bioavailability of digoxin. Genetic polymorphisms within this gene might modify the risk of sudden cardiac death (SCD).

Objectives: The aim of this study was to investigate the interaction between variants within the ABCB1 gene and digoxin on the risk of SCD.

Methods: Within the Rotterdam Study, a population-based cohort study in persons 45 years of age and older, we used Cox regression to analyze the effect of three frequently studied and relevant polymorphisms extracted from 1000-genomes imputed ABCB1 genotypes (C1236T, G2677T, and C3435T) on the risk of SCD, stratified by digoxin use. We adjusted the analyses for age, sex, smoking, heart-rate corrected QT interval, and prevalent heart failure, coronary heart disease, and atrial fibrillation.

Results: In a total study population of 10 932 persons, 419 SCDs occurred during a median follow-up of 9.8 years. At baseline, the mean age was 65.2 ± 9.6 years, and 42% was male. In nonusers of digoxin, the risk of SCD was not different across genotypes. In digoxin users, homozygous T allele carriers of C1236T (HR 1.90; 95%CI 1.09;3.30; allele frequency 0.43), G2677T (HR 1.89; 95%CI 1.10;3.24; allele frequency 0.44), and C3435T (HR 1.72; 95%CI 1.03;2.87; allele frequency 0.53) had a significantly increased risk of SCD in a recessive model. Interaction between the ABCB1 polymorphisms and digoxin use was significant for C1236T ($p = 0.04$) and G2677T ($p = 0.03$) in the age and sex adjusted model.

Conclusions: In this study, we showed that in digoxin users, homozygous T allele carriers of the ABCB1 gene had an increased risk of SCD compared with digoxin users with none or one T allele. This implies that the ABCB1 genotype modifies the risk of cardiac digoxin toxicity. If these findings can be replicated in an independent cohort, testing ABCB1 gene variants in new users of digoxin could enhance safe use of this drug if drug concentration monitoring alone is insufficient to reduce the associated risk in a specific group of patients.

359. A CACNA1C Variant Is Associated with a Modified Response of Heart Rate in Users of Calcium Channel Blockers: The Rotterdam Study

Maartje N Niemeijer, Marten E van den Berg, Albert Hofman, Oscar H Franco, Andre G Uitterlinden, Jan A Kors, Bruno H Stricker, Peter R Rijnbeek, Mark Eijgelsheim. *Erasmus MC - University Medical Center Rotterdam, Rotterdam.*

Background: Diltiazem and verapamil reduce heart rate by blocking the calcium current into cells through calcium channels, which are encoded by the CACNA1C gene. A variant within this gene, rs2238018, has recently been found to explain part of the variability in resting heart rate.

Objectives: The aim of this study was to study whether rs2238018 modifies the effect of diltiazem and verapamil on heart rate.

Methods: Our study population was taken from a population-based cohort of persons aged 45 years and older, with up to five electrocardiograms recorded per participant between 1991 and 2010. We used generalized estimating equations to study the interaction between rs2238018 status and diltiazem or verapamil use on heart rate and occurrence of bradycardia, defined as a heart rate lower than or equal to 60 beats per minute. The analyses were adjusted for age, sex, duration, dosage, and a history of coronary heart disease and diabetes mellitus.

Results: The study population consisted of 9424 participants with 18 450 electrocardiograms: 269 during diltiazem use and 108 during verapamil use. The mean age at baseline was 65.0 ± 9.7 years, and 58.4% were women. The rs2238018 polymorphism showed significant interaction with diltiazem and verapamil on heart rate ($p = 0.04$). Each T allele (frequency 19.6%) was associated with progressively lower heart rates in users: −2.52 beats per minute (95%CI −5.44; 0.40) in diltiazem users and −4.29 beats per minute (95% CI −7.96; −0.61) in verapamil users. No effect of the polymorphism was seen in nonusers. Homozygous minor allele carriers using either diltiazem or verapamil had a 4.64-fold increased risk (95%CI 1.40; 15.41) of bradycardia compared with homozygous major allele carriers.

Conclusions: In this study, T allele carriers of the rs2238018 polymorphism have a stronger response to

diltiazem and verapamil with respect to heart rate. Knowledge of rs2238018 status might be clinically relevant as heart-rate reduction can be either the objective of treatment or an adverse effect and might add to the future ambitions of tailored pharmacotherapy with diltiazem and verapamil; however, further studies on clinical relevant endpoints are needed.

360. Appropriateness and Persistence of Testosterone Replacement Therapy in the Public Payer System

Diana Martins,[1] Mina Tadrous,[2] Zhan Yao,[1] Baiju R Shah,[1] David Juurlink,[1] Muhammad Mamdani,[2] Tara Gomes.[2] *[1]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [2]Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON, Canada.*

Background: Rates of prescribing for testosterone replacement therapy (TRT) products have been increasing in Ontario, Canada, despite criteria in the public drug formulary, which limit TRT to males with confirmed low serum testosterone levels associated with documented and symptomatic hypothalamic/pituitary/testicular disease or in HIV-infected patients.

Objectives: The objectives of this study were to evaluate the degree to which prescribing of TRT through the Ontario Drug Benefit program aligns with current prescribing criteria and to compare persistence between available formulations.

Methods: We conducted a retrospective cohort study of publicly funded testosterone utilization among males aged 66 years or older in Ontario between January 2009 and December 2013 using linked health administrative data. All males newly prescribed a testosterone product during the study period were included, and comparisons between TRT formulations were made among continuous users (individuals with a subsequent prescription within 180 days). We estimated the prevalence of hypogonadism and HIV and lab tests for serum testosterone in the year prior to therapy initiation. We also conducted a Kaplan–Meier analysis to test for differences in the median duration of therapy.

Results: Among the 6728 males initiating TRT over the study period, 47.5% of injectable users, 30.9% of transdermal patch users, 23.4% of topical users, and 22.8% of oral users received only one prescription. Among the 4797 continuous users, between 5.4% and 15.4% of users had a diagnosis of hypogonadism, and less than 1% had a diagnosis of HIV. Furthermore, the number of users with no prior testosterone lab test ranged from 29.0% for topical users to 39.5% for injectable users. The median duration of TRT differed significantly across formulations and was highest among oral users (383 days) compared with topical (319 days), injectable (283 days), and transdermal patch (160 days; $p < 0.001$) users.

Conclusions: A large proportion of older men in Ontario are initiating and remaining on TRT without meeting the listing criteria. Given the cardiovascular safety concerns of TRT, changes in listing of testosterone products should be considered to reduce inappropriate prescribing.

361. Patterns of Angiotensin Converting Enzyme Inhibitor Prescriptions for Different Indications: A Population-based Study

Seyed Hamidreza Mahmoudpour,[1] Folkert W Asselbergs,[2,3,4] Patrick C Souverein,[1] Anthonius de Boer,[1] Anke-Hilse Maitland-van der Zee.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands; [2]Department of Cardiology, Division Heart and Lungs, University Medical Centre Utrecht, Utrecht, The Netherlands; [3]Durrer Center for Cardiogenetic Research, ICIN-Netherlands Heart Institute, Utrecht, The Netherlands; [4]Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, UK.*

Background: Angiotensin converting enzyme inhibitors (ACEIs) are widely prescribed. While ACEIs are usually initiated for lifelong treatment, many patients stop or switch treatment. Exploration of such patterns is important because the discontinuation of these drugs is associated with poor clinical outcomes.

Objectives: The aim of this study was to study usage patterns for different indications of ACEIs.

Methods: We defined a cohort of patients older than 45 years who started ACEI treatment between 2007 and 2013 in the Clinical Practice Research Datalink (CPRD). Indications for ACEI treatment (hypertension

(HTN), heart failure (HF), myocardial infarction (MI), renal failure (RF), or combinations of them (COT)) were retrieved from the medical records, and duration of ACEI treatment was calculated. We distinguished between continuous use, discontinued use, switch to an alternative drug, and restart, considering 6 months time interval between two prescription periods. Five-year persistence among the different indications was calculated using the Kaplan–Meier method, and times to discontinuation were compared using the log-rank test.

Results: In total, 222 058 patients initiating ACEIs were identified with the following indications: HTN (68.2%), MI (5.1%), RF (4.4%), HF (1.9%), and COT (20.4%). Five-year persistence rates were 62.4% for HF, 58% for HTN, 70.1% for MI, 45.5% for RF, and 55% for COT. Time to discontinuation was significantly different between indications (log-rank p-value < 0.0001). RF patients used ACEIs for the shortest period of time (average 23 months and median 13 months). Within the discontinuation group for different indications, the percentage of total switchers ranged from 37.6% for RF to 56.2% for HTN patients. For the patients who restarted, the percentages ranged from 12.6% for HF to 16.7% for RF patients. Of the 42 327 switchers, 58.6% switched to an angiotensin receptor blocker (ARB), which varied for different indications from 56.2% for HTN to 78.6% for MI patients.

Conclusions: Dependent on indication, there are different rates of discontinuation of ACEIs and switching to ARBs. Patients with RF are most vulnerable to discontinue treatment.

362. Methodological Issues in Harmonizing Data from Electronic Health Record Systems for International Pharmacosurveillance

Robyn Tamblyn,[1] David W Bates,[2] William Dixon,[3] Michal Abrahamowicz,[1] Nadyne Girard,[1] Jennifer Haas.[2] *[1]Epidemiology, Biostatistics & Occupational Health/Medicine, McGill University, Montreal, QC, Canada; [2]Brigham & Women's Hospital, Boston, MA, USA; [3]University of Manchester, Manchester, UK.*

Background: Electronic health records (EHRs) are creating unprecedented opportunities to develop near real-time international pharmacosurveillance systems. To harness this potential, a variety of methodological issues need to be addressed, including data harmonization and the comparability of populations and health systems.

Objectives: The aim of this study was to estimate the impact of using (1) prescribed relative to dispensed prescription data to measure drug exposure, (2) diagnostic code-based versus clinical enriched data to assess co-morbidities, and (3) national differences in prescribing practices on the risk of cardiovascular events (CVE) with different hypoglycemic therapies in a population of newly treated diabetics.

Methods: EHRs from Britain, Canada, and the United States were used to assemble a cohort of 45 129 newly treated diabetics between 2011 and 2013. Time-varying measures of hypoglycemic use were created from prescription data and compared with dispensing data, as were national differences in drug use within therapeutic class. Obesity, renal impairment, and hyperlipidemia were measured using diagnostic codes and compared with enriched measures using clinical data. Cox proportional hazards models were used to assess the impact of different methodological approaches to risk assessment.

Results: Twenty-five percent of prescriptions were never filled, resulting in biased estimates of the effect of non-drug use on the risk of cardiovascular events. There were fourfold increases in the prevalence of obesity using BMI (13% to 60%), renal impairment using creatinine (12% to 47%), and lipid disorders (16% to 47%), but had no impact on confounding related to drug exposure. There was a twofold increase in the risk of CVE with sulfonylureas in the United States (HR: 3.3 95%CI: 2.0–5.5) compared with Britain (HR:1.4 95%CI: 1.1–1.7), which may be explained by substantial differences in the sulfonylureas used in Britain.

Conclusions: EHRs can improve measurement of drug exposure and morbidity and elucidate potentially important differences in the risk of drug use in different countries.

363. Pharmacy Drug Dispensing after Physician Discontinuation Orders

Tewodros Eguale,[1,2,3,4] Aman Verma,[4] Enrique Seoane-Vazquez,[1,2] David W Bates,[2,3] Robyn Tamblyn,[4] Gordon D Schiff.[2,3] *[1]Pharmacoeconomics and Policy, MCPHS University, Boston, MA, USA; [2]Division of General Medicine and Primary Care, Brigham and Women Hospital, Boston, MA, USA;*

[3]*Harvard School of Medicine, Boston, MA, USA;* [4]*Clinical and Health Informatics Research Group, McGill University, Montreal, QC, Canada.*

Background: Physicians discontinue previously prescribed drugs because of considerations of safety and effectiveness, but it is unclear what effect these discontinuation orders have on pharmacy dispensing. New electronic health records (EHR) allow us to monitor discontinuation orders, discontinuation reasons, and actual dispensation data.

Objectives: Using data from an EHR, we assessed the frequency of pharmacy drug dispensation after physician discontinue orders and modeled how the discontinuation reasons affected pharmacy dispensation.

Methods: We conducted the study in two Canadian cities where family physicians use the MOXXI EHR, which allows physicians to prescribe and discontinue drugs and send the information to the pharmacy. We included all discontinuation orders issued between 2005 and 2012 for patients fully covered by provincial drug insurance. Using logistic regression, we modeled pharmacy dispensation of discontinued drugs within 12 months of the discontinuation order as a function of the discontinuation reasons and patient and drug characteristics.

Results: Between 2005 and 2012, there were 40 452 drug discontinuation orders, of which, 7325 (18.1%) were dispensed within 12 months (75% within the first month). Many drugs were discontinued because they were "no longer necessary" (27.3%), ineffective (18.7%), or caused adverse drug events (18.2%). Drugs discontinued because of adverse drug event [OR: 0.7 95%CI: (0.7–0.8)] and allergic reaction [OR: 0.6 95%CI: (0.4–1.0)] had low risk of dispensation compared with drugs stopped because they were "no longer necessary," while drugs discontinued because they were ineffective had a higher odds [OR: 1.3 95%CI: (1.2–1.5)]. Compared with gastrointestinal drugs, central nervous system drugs [OR: 1.5 95% CI: (1.3–1.6)] and cardiovascular drugs [OR: 1.1 95%CI: (1.0–1.2)] had higher odds of dispensation, and anti-infective drugs had lower odds [OR: 95%CI: 0.5 (0.4–0.6)].

Conclusions: Patient safety may have been compromised when discontinued drugs were dispensed to patients, especially those discontinued because of an adverse drug reaction. The next generation of electronic health records should better integrate with the pharmacy, to avert dispensation of discontinued drugs.

364. Use of Prescription Drug Samples in the United States and Implications for Pharmacoepidemiologic Studies

Christian Hampp, Patty Greene, Simone P Pinheiro. *Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA.*

Background: Free prescription drug samples dispensed in physician offices can lead to exposure misclassification in pharmacoepidemiologic studies that rely on pharmacy claims data.

Objectives: The aim of this study was to estimate the extent of sample provisions between branded and generic drugs within several chronic and acute indications and by type of prescription drug benefits.

Methods: We extracted nationally projected drug-specific information on sample provisions during new and continued therapy from a survey of over 3200 office-based physicians for 1993–2013. We selected medications with chronic (diabetes, hyperlipidemia, hypertension, anticoagulation, attention deficit/hyperactivity disorder, oral contraceptives (OCs)), and acute indications (oral and ophthalmic antibiotics).

Results: Between 2009 and 2013, 41.4% of new sitagliptin therapy but only 3.1% of new metformin therapy were provided as samples. We observed similar discrepancies between branded and generic drug pairs: rosuvastatin and simvastatin, dabigatran and warfarin, atomoxetine and methylphenidate, and between antibiotic drugs. Samples were very common for some newly initiated OCs (norethindrone, 73.7%). During continued use, sample use was still present (sitagliptin, 7.9%; rosuvastatin, 13.9%) and remained high for some OCs (norethindrone, 52.0%). From 1993 to 2013, we found pronounced drops in sample use coinciding with more recent generic approval dates. Sample provision rates in new therapy tended to be lower among Medicaid recipients and higher in patients with private insurance in some instances and in patients without any insurance in other instances. OCs had the longest days of sample supply (levonorgestrel continued use,

85.2 days). All other chronically used study drugs ranged from 13.4 days (dabigatran, new use) to 25.3 days (exenatide, continued use).

Conclusions: Markedly differential exposure to medication samples between branded and generic drugs can introduce bias in pharmacoepidemiologic studies, especially in studies on adverse events that occur soon after drug initiation. These findings may help inform the potential for misclassification in pharmacoepidemiologic studies that rely on pharmacy claims data.

365. Exposure Mapping of Antimicrobials for the Treatment of Methicillin-resistant Staphylococcus aureus (MRSA) Bacteremia

Aisling R Caffrey,[1,2] Eunsun Noh,[1,2] Kerry L LaPlante.[1,2] *[1]Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA; [2]College of Pharmacy, University of Rhode Island, Kingston, RI, USA.*

Background: Measuring antibiotic exposures is difficult because patients often receive complex treatment regimens with multiple agents for short periods of time. As a result, most research focuses on patients receiving monotherapy, which provides a limited view of infectious disease pharmacotherapy.

Objectives: The aim of this study was to describe real-world treatment regimens for MRSA bacteremia using exposure mapping.

Methods: This national retrospective cohort study included patients admitted to Veterans Affairs hospitals with MRSA isolates from blood cultures between January 2004 and October 2012. Pharmacy data were assessed from hospital barcode medication administration records, as well as inpatient and outpatient dispensings. We mapped antibiotic exposures for each patient on each day of the admission. Antibiotics with activity against MRSA, as well as adjunctive therapies, were assessed. Following the mapped exposure timeline for each patient, we identified initial therapy, as well as therapy additions, switches, and discontinuations, and each was categorized as monotherapy or combination therapy.

Results: Of the 16 175 MRSA bacteremia patients included in our study, 20% had no change to their initial treatment. The most frequent initial treatment was vancomycin plus beta-lactams (VAN + BL, 24%), followed by beta-lactam (BL, 20%), vancomycin (VAN, 19%), and fluoroquinolone (FLQ, 10%) monotherapy. Among VAN + BL patients, 62% ($n = 2390$) dropped one of the therapies while continuing on the other, with most (54%) continuing on VAN. Switching was observed in 7% ($n = 279$; most common: FLQ 24%, linezolid 14%) and additions in 17% ($n = 656$; most common: FLQ 28%, gentamicin 12%). Of patients initiating BL, 77% ($n = 2506$) had therapy additions, mostly vancomycin ($n = 2049$, 82%). Among VAN patients, 43% ($n = 1319$) had changes to therapy, while 45% ($n = 1392$) had therapy additions (most common: BL 43%, FLQ 13%, rifampin 8%).

Conclusions: To our knowledge, this is the first exposure mapping study to identify all MRSA bacteremia treatment patterns in a large national cohort. Characterizing these real-world treatment regimens will allow us to conduct more meaningful comparative effectiveness and safety research.

366. Utilization of Antipsychotics and Stimulants during Pregnancy among Publicly Insured Women in the United States

Yoonyoung Park,[1,2] Sonia Hernández-Díaz,[2] Brian T Bateman,[1,3] Elisabetta Patorno,[1] Rishi J Desai,[1] Helen Mogun,[1] Krista F Huybrechts.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [3]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA.*

Background: Up to 25% of pregnant women have a psychiatric disorder. While a number of studies have focused on the use and safety of antidepressants, fewer studies have investigated the use of other psychotropic medications indicated for conditions such as schizophrenia, bipolar disorder, and attention-deficit hyperactivity disorder (ADHD).

Objectives: The aim of this study was to examine utilization patterns of antipsychotics and stimulants during pregnancy among publicly insured women in the United States.

Methods: We used nationwide claims data from pregnant women covered by Medicaid in 2000–2010,

with continuous enrollment from 3 months prior to pregnancy to 1 month after delivery. The proportions of women who had a pharmacy dispensing record for an antipsychotic or stimulant at any time during pregnancy were calculated. Patient characteristics as well as regional and temporal trends were explored.

Results: Among 1 356 514 eligible women with liveborn infants, the proportion receiving any antipsychotic or stimulant was 0.9% ($N = 12\,673$) and 0.5% ($N = 6949$), respectively. The proportion for atypical antipsychotics increased from 0.6% in 2000 to 1.3% in 2010 (p-trend < 0.0001); for typical antipsychotics, from 0.07% to 0.1% (p-trend $= 0.7$); and for stimulants, from 0.1% to 0.9% (p-trend < 0.0001) over the same period. Quetiapine (45.8%) and risperidone (18.4%) were the most frequently dispensed atypical antipsychotics, and amphetamine/dextroamphetamine (46.6%) and methylphenidate (22.7%) were the most common stimulants. Overall, the proportion varied between states, ranging from 0.4% to 7.0% for antipsychotics and from 0.09% to 1.8% for stimulants. Women receiving these drugs were generally older, white, and had a greater number of comorbidities and co-medications.

Conclusions: The proportions of pregnant women treated with antipsychotics and stimulants increased by twofold and ninefold, respectively, during the last decade in the publically insured US population. Large regional variability in use was observed. The frequency with which these medications are used in pregnancy warrants further study on the safety of these drugs.

367. Antipsychotic Medication Use during Pregnancy and Risk of Congenital Cardiac Malformations

Krista F Huybrechts,[1] Brian T Bateman,[1,2] Elisabetta Patorno,[1] Rishi Desai,[1] Helen Mogun,[1] Sonia Hernandez-Diaz.[3] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: The use of antipsychotic medications (APMs), in particular atypicals, in pregnancy has increased rapidly over time, from one in 166 publicly insured pregnant woman being exposed in 2000, to one in 78 women in 2010. Yet, little is known about their safety for the neonate.

Objectives: The aim of this study was to examine the risk of cardiac malformations associated with first trimester exposure to different APMs.

Methods: We conducted a cohort study nested in 2000–2010 nationwide Medicaid data, including 1 356 514 pregnant women with a liveborn infant who were publicly insured from 3 months before pregnancy through at least 1 month post delivery. We compared the risk of cardiac malformations (based on recorded ICD-9 diagnoses, using a validated algorithm) among infants born to women who were dispensed an APM during the first trimester versus no use. We stratified on propensity scores (100 strata) to control for psychiatric morbidity and a broad range of other potential confounders.

Results: 9876 (0.73%) women filled at least one prescription for an atypical APM; 798 (0.06%) for a typical APM. Overall, 15/1000 births not exposed to APMs were diagnosed with cardiac malformations, compared with 23/1000 births exposed to atypical and 26/1000 births exposed to typical APMs. Unadjusted associations were RR = 1.54 (95%CI 1.35–1.76) for atypical APMs, and 1.75 (1.13–2.69) for typical APMs. Except for olanzapine (1.01, 95% CI 0.67–1.52), unadjusted risks were significantly increased for all individual atypical APMs: 1.45 (1.06–1.97) for aripiprazole, 1.65 (1.37–1.99) for quetiapine, 1.70 (1.26–2.30) for risperidone, and 1.97 (1.29–3.01) for ziprasidone. Associations were greatly attenuated after confounding adjustment: RR = 1.08 (0.87–1.34) for atypical APMs, 1.29 (0.70–2.36) for typical APMs, 1.16 (0.71–1.88) for aripiprazole, 0.59 (0.28–1.25) for olanzapine, 1.04 (0.74–1.44) for quetiapine, 1.24 (0.80–1.93) for risperidone, and 1.60 (0.83–3.09) for ziprasidone.

Conclusions: Results of the largest cohort study to date suggest no substantial increased risk of cardiac malformations attributable to APMs overall, but the possibility that individual agents confer an increased risk cannot be excluded.

368. Attention Deficit Hyperactivity Medications during Pregnancy and the Risk of Congenital Cardiac Malformations: A Cohort Study

Brian T Bateman,[1,2] Krista F Huybrechts,[1] Elisabetta Patorno,[1] Rishi Desai,[1] Sonia Hernandez-Diaz.[3] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder in children, which is increasingly being recognized as having the potential to extend into adulthood. As such, it is important to understand the teratogenic risk of drugs commonly used to treat ADHD.

Objectives: The aim of this study was to define the risk of cardiac malformation associated with first trimester exposure to two of the most commonly used ADHD medications: amphetamine-dextroamphetamine and methylphenidate.

Methods: We used a cohort of 1 356 514 completed pregnancies linked to liveborn infants of women enrolled in Medicaid from 2000 to 2010. We examined the risk of major cardiac malformations associated with first trimester exposure to amphetamine-dextroamphetamine and methylphenidate, which was defined based on a filled prescription during this exposure window. The reference group consisted of women without exposure to these medications during the first trimester. Propensity score stratification (100 strata of fixed score interval) was used to control for potential confounders including maternal demographics, obstetric and medical conditions, and exposure to other medications.

Results: There were 3068 (0.2%) women dispensed amphetamine-dextroamphetamine and 1437 (0.1%) dispensed methylphenidate during the first trimester. The risk of cardiac malformations in the amphetamine-dextroamphetamine exposed was 1.92% and 2.78% in the methylphenidate exposed compared with 1.53% in the non-exposed. After controlling for confounders, the relative risk for cardiac malformations was 0.81 (95%CI 0.44 to 1.50) for amphetamine-dextroamphetamine and 2.08 (95%CI 1.26 to 3.44) for methylphenidate.

Conclusions: The results of this preliminary analysis suggest that maternal use of methylphenidate in the first trimester may be associated with an approximately twofold increase in the risk of major cardiac malformations, independent of measured confounders. Amphetamine-dextroamphetamine was not associated with elevated risk.

369. The Safety of Mood Stabilizers in Pregnant Women with Regard to the Risk of Congenital Cardiac Malformations

Elisabetta Patorno,[1] Krista Huybrechts,[1] Brian Bateman,[1,2] Rishi Desai,[1] Helen Mogun,[1] Sonia Hernández-Díaz.[3] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: Mood disorders in women of childbearing age often require pharmacologic treatment, including lithium and specific anticonvulsant drugs such as valproate. One potential concern is the increased risk of congenital cardiac abnormalities associated with maternal use of specific mood stabilizers (MSs) during pregnancy.

Objectives: The aim of this study was to assess the risk of cardiac malformation associated with maternal use of MSs.

Methods: Our population included 1 356 514 women who delivered a liveborn infant during 2000–2010 and were enrolled in Medicaid from 3 months before conception to 1 month after delivery. We examined the risk of cardiac malformations (identified through a validated claims-based algorithm) associated with first trimester pharmacy dispensing of specific MSs, compared with that among women unexposed to either lithium or anticonvulsants. Fine stratification on propensity score (100 strata) was used to control over 50 baseline characteristics, including indications and other potential confounders, among exposed and unexposed women. Relative risks (RR) and 95% confidence intervals (CI) were calculated.

Results: During the first trimester, 956 women filled at least one prescription for lithium (0.07%), 1507 for carbamazepine (0.11%), 2647 for valproate (0.20%), and 2841 for lamotrigine (0.21%). The unadjusted RR for cardiac malformations was 1.86 (95%CI

1.28–2.70) for lithium, 1.75 (1.29–2.38) for carbamazepine, 2.07 (1.67–2.56) for valproate, and 1.46 (1.14–1.87) for lamotrigine. The adjusted RR was 2.56 (95% CI 1.53–4.29) for lithium, 0.60 (0.20–1.83) for carbamazepine, 1.44 (0.96–2.16) for valproate, and 0.91 (0.57–1.47) for lamotrigine. Results were consistent when we restricted to women who used MSs in monotherapy, with RR = 2.62 (1.54–4.46) for lithium, 0.71 (0.24–2.17) for carbamazepine, 1.56 (1.03–2.36) for valproate, and 0.95 (0.59–1.55) for lamotrigine.

Conclusions: Preliminary results from this large nationwide investigation suggest that once confounding was controlled, lithium and valproate may be associated with an increased risk of cardiac malformations. CIs for carbamazepine were too wide to allow conclusions.

370. Effect of Selective Serotonin Reuptake Inhibitor (SSRI) Exposure during Pregnancy on Birth Weight and Gestational Age: A Sibling-controlled Cohort Study

Katerina Nezvalova-Henriksen,[1] Olav Spigset,[2,3] Ragnhild Eek Brandlistuen,[1,4] Eivind Ystrom,[5] Gideon Koren,[6] Hedvig Nordeng.[1,7] *[1]Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway; [2]Department of Clinical Pharmacology, St Olav's University Hospital, Trondheim, Norway; [3]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; [4]Department of Child Development and Mental Health, Norwegian Institute of Public Health, Oslo, Norway; [5]Department of Genetics, Environment and Mental Health, Norwegian Institute of Public Health, Oslo, Norway; [6]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada; [7]Department of Psychosomatics and Health Behavior, Norwegian Institute of Public Health, Oslo, Norway.*

Background: Studies on the effects of SSRI-antidepressants on birth weight and gestational age remain conflicting. Using a cohort design, we previously found that exposure to antidepressants was not associated with increased risk of preterm birth or low birth weight in the Norwegian Mother and Child Cohort. In an attempt to adjust for shared genetics and family environmental factors, we now wish to employ a sibling design to study these associations *de novo*.

Objectives: The aim of this study was to use a sibling design to determine whether prenatal SSRI exposure is associated with birth weight and gestational age.

Methods: Sibling-control analysis via linkage of the Norwegian Mother and Child Cohort Study (information on prenatal antidepressant exposure) to the Medical Birth Registry of Norway (information on birth weight and gestational age) was performed. We performed unmatched sibling analyses and matched sibling analyses using random-effects and fixed-effects linear models, respectively, to determine potential effects of antidepressant exposure on birth weight and gestational age.

Results: Of 27 756 eligible siblings, 194 were prenatally exposed to SSRI-antidepressants, 1994 had mothers with persisting symptoms of depression without exposure to antidepressants, and 25 022 had non-depressed mothers. Exposure to SSRI-antidepressants anytime during pregnancy was not associated with birth weight or gestational age. Third trimester exposure was associated with gestational age even after adjustment for maternal symptoms of depression and other confounding factors: adjusted β −0.86, 95%CI (−1.41 to −0.31).

Conclusions: Our sibling study shows that SSRI-antidepressants were not associated with lower birth weight but with a shorter gestation after adjustment for family-level confounding and maternal symptoms of depression.

371. First Trimester Exposure to Citalopram and the Risk of Major Congenital Malformations in a Cohort of Depressed Women

Jin-Ping Zhao, Odile Sheehy, Noha Iessa, Anick Bérard. *CHU Ste-Justine, Montreal, Canada; University of Montreal, Montreal, Canada.*

Background: Selective serotonin reuptake inhibitors (SSRI) were widely prescribed during pregnancy. Few have studied the teratogenic risk associated with the use of citalopram, an SSRI, during the first trimester.

Objectives: The aim of this study was to quantify the association between first trimester exposure to citalopram and the risk of congenital malformations in a cohort of depressed women.

Methods: This study was performed within the Quebec Pregnancy Cohort and includes all

pregnancies covered by the Quebec drug plan between 1998 and 2010. To be eligible for this study, women had to (1) have a diagnosis of depression, (2) be using only one type of antidepressant during the first trimester, and (3) have a live birth. Depressed pregnant women not using antidepressants during pregnancy were the reference category. Citalopram use during the first trimester, non-citalopram SSRI use and non-SSRI use were the exposure categories. Major congenital malformations overall and organ-specific malformations in the first year of life were identified. Generalised estimating equation (GEE) models were used to obtain odds ratios (OR) and 95% confidence intervals (CI), taking into account potential confounders.

Results: Among the 18 493 eligible pregnancies, 587 were exposed to citalopram, 1742 to non-citalopram SSRIs and 1296 to non-SSRI antidepressants during the first trimester of pregnancies; 2094 infants with major congenital malformations were identified, 92 had cranyosynostosis and 800 had musculoskeletal defects. Citalopram use was statistically significantly (OR 1.42, 95%CI: 1.12–1.7; 90 exposed cases) associated with the risk of overall major malformations when compared with non-use in depressed pregnant women. Citalopram exposure during the first trimester of pregnancy was also associated with an increased risk of craniosynostosis (OR 4.21, 95%CI: 2.14–8.28; 10 exposed cases), and musculoskeletal defects (OR 1.92, 95%CI: 1.41–2.63; 46 exposed cases).

Conclusions: Citalopram use during the first trimester of pregnancy was associated with an increased risk of overall major malformations, cranyosinostosis and musculoskeletal defects above and beyond the effect of maternal depression.

372. The Medicines Advice Service Evaluation (MASE): An RCT of an Intervention to Improve Medication Adherence in a Mail-order Pharmacy Population

Imogen Lyons,[1] Nick Barber,[2] DK Raynor,[3] Li Wei.[1]
[1]Practice and Policy, School of Pharmacy, University College London, London, UK; [2]The Health Foundation, London, UK; [3]University of Leeds, Leeds, UK.

Background: Non-adherence to medicines for long-term conditions is a complex, prevalent phenomenon, with significant clinical and economic consequences for patients and health providers worldwide.

Objectives: The aim of this study was to test the effectiveness of a pharmacist-led intervention to improve adherence, in the context of mail-order pharmacy.

Methods: A parallel-group RCT was conducted. Six hundred seventy-seven patients prescribed at least one oral medication for type 2 diabetes and/or lipid regulation were recruited from a UK mail-order pharmacy between November 2012 and September 2013, and randomised (340 interventions and 337 controls). The intervention was patient-centred, comprising information and advice by phone and written information by post, delivered by a pharmacist. All elements of the intervention were tailored to the individuals' needs. The primary outcome was self-reported adherence to medication at 6-month follow-up, measured using the Diagnostic Adherence to Medication Scale. Generalised estimating equations analyses were conducted according to the intention-to-treat principle. Secondary outcomes included prescription refill adherence defined as a medication possession ratio and lipid and glycemic control.

Results: Patients who received the intervention had 54% increased odds of being adherent (defined as ≥90% of medication taken in the past 7 days), compared with the control group (OR 1.54, 95%CI 1.11–2.15, $p = 0.01$). Analyses of dispensing data also showed that the odds of being classified as adherent (≥90%) were 60% greater for the intervention group compared with the control group (OR 1.60, 95%CI 1.14–2.24, $p < 0.01$). For patients who provided a blood sample at 6-month follow-up, 67% vs 31% (16 interventions, five controls, $p = 0.06$) and 65% vs 55% (64 interventions, 38 controls, $p = 0.24$) achieved guideline targets for glycemic and lipid control, respectively.

Conclusions: Intervention, led by a pharmacist and tailored to the individuals' needs, can significantly improve medication adherence in patients with long-term conditions. The findings provide further support for the enhanced role of pharmacists in supporting and advising patients with their medicines and improving outcomes.

373. Taking Medication Adherence Personally: What Does Prior Adherence Tell Us about Future Adherence?

Stacie B Dusetzina,[1,2] Aaron N Winn.[2] *[1]Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Gillings School*

of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

Background: Medication non-adherence is estimated to cost the USA nearly $290bn annually. Efforts to better monitor patient medication-taking behaviors are underway, including the prospective use of health plan claims for intervening on patients who are at risk of poor adherence. One key question is whether patient adherence to one drug is related to their adherence to other drugs: simply, is adherence an intrapersonal characteristic where prior adherence could be used to predict "normal" adherence for a particular patient?

Objectives: We used group-based trajectory models to examine the association between adherence patterns for two types of therapy for patients with breast cancer—endocrine therapy (ET) and statins—to determine the extent to which medication-taking behaviors are similar across products.

Methods: We used SEER-Medicare data to identify women with breast cancer who initiated ET between 2007 and 2009 and who initiated statins at least 1 year prior to ET ($N=2593$). We used group-based trajectory models to estimate 12-month medication adherence to each therapy separately. We estimated the extent to which patients were categorized in similar treatment trajectories across both products using binomial regression.

Results: We found four statin adherence groups: quick stops (8.8%), quick decline with continued low use (16.1%), gradual decline (30.8%), and consistently high (44.3%). Similarly, ET users were grouped as quick stops (16.0%), quick decline with gradual increase (17.7%), gradual decline (19.6%), and consistently high (46.9%). Women highly adherent to statins in the year prior to ET initiation were 33% more likely to be highly adherent to ET as compared with women with other statin adherence trajectories (RR:1.33, CI:1.23–1.44). Additionally, women who quickly stopped statins were more likely to quickly stop ET (RR:1.49, CI:1.15–1.92).

Conclusions: Prior adherence to medications may be useful for identifying expected adherence behaviors for patients initiating new therapies. Discordant adherence patterns may indicate safety or tolerability concerns and should be further investigated.

374. Using Machine Learning to Examine Medication Adherence Thresholds and Risk of Hospitalization

Wei-Hsuan Lo-Ciganic,[1] Julie M Donohue,[2] Joshua M Thorpe,[3,4] Subashan Perera,[5,6] Carolyn T Thorpe,[3,4] Zachary A Marcum,[7] Walid F Gellad.[4,6] *[1]College of Pharmacy, University of Arizona, Tucson, AZ, USA; [2]Department of Health Policy and Management, University of Pittsburgh, Pittsburgh, PA, USA; [3]Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA, USA; [4]Center for Health Equity Research and Geriatric Research Education and Clinical Center, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, USA; [5]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA; [6]Department of Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [7]School of Pharmacy, University of Washington, Seattle, WA, USA.*

Background: Quality improvement efforts for chronic diseases, and associated financial incentives, are frequently tied to patients achieving ≥80% annual medication refill adherence. However, little empirical evidence exists that this threshold optimally predicts health outcomes overall or within different patient subgroups.

Objectives: The objectives of this study were to apply machine learning to examine how adherence to oral hypoglycemic medications is associated with avoidance of hospitalizations in diabetes patients and to identify adherence thresholds for optimal discrimination of hospitalization risk.

Methods: A retrospective cohort study of 33 130 Pennsylvania Medicaid enrollees aged 18–64 years with type 2 diabetes and ≥2 oral hypoglycemic prescriptions between 2007 and 2009 was carried out. We randomly selected 90% of the cohort (training sample) to develop the prediction algorithm and used the remaining (testing sample) for algorithm validation. Refill adherence was calculated using proportion of days covered (PDC) for oral hypoglycemics over 1 year. We applied random survival forests to identify predictors for time to first all-cause hospitalization in the subsequent year and fit survival trees to empirically derive adherence thresholds that best discriminate hospitalization risk.

Results: The training and testing samples had similar characteristics (mean age, 48 years; 67% female; 51% whites; mean PDC, 0.65; and 24% hospitalization rate). We identified eight important predictors of all-cause hospitalizations (ranked in order): prior hospitalizations or emergency department visits, number of monthly prescriptions, diabetes

complications, insulin use, PDC, number of prescribers, Elixhauser index, and Medicaid eligibility category. The adherence thresholds most discriminating for risk of all-cause hospitalization varied from 46% to 94% according to patient health and medication complexity. PDC was not predictive of subsequent hospitalizations in the healthiest or most complex patient subgroups.

Conclusions: Adherence thresholds most discriminating of hospitalization risk were not uniformly 80%. Machine learning approaches are valuable for identifying appropriate disease/patient-specific thresholds for measuring quality of care.

375. Observing Versus Predicting: Initial Patterns of Filling Predict Long-term Adherence More Accurately Than High-dimensional Modeling Techniques

Jessica Franklin,[1] William Shrank,[2] Joyce Lii,[1] Alexis Krumme,[1] Olga Matlin,[2] Troyen Brennan,[2] Niteesh Choudhry.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]CVS Caremark, Woonsocket, RI, USA.*

Background: Despite the proliferation of databases with increasingly rich patient data, prediction of medication adherence remains poor. Traditional approaches use clinical and demographic information available at the time of treatment initiation; because adherence is a complex behavior, using observed patterns of initial refilling may provide a better alternative.

Objectives: The aim of this study was to evaluate the ability of new data sources, advanced analytic techniques, and post-initiation filling behavior to improve prediction of adherence to statins.

Methods: We identified Medicare beneficiaries who received prescription drug coverage through CVS Caremark and initiated a statin. A total of 643 variables were identified at baseline from prior claims and linked census data. In addition, we identified three post-baseline predictors, consisting of indicators of full adherence (PDC $\geq$ 0.8) to statins during each of the first 3 months of follow-up. We estimated 10 models predicting the binary indicator of PDC $\geq$ 0.8 during follow-up, using logistic regression and boosted logistic regression, a nonparametric data-mining technique. Models were also estimated within strata defined by the index days supply.

Results: In 77 703 statin initiators, prediction using baseline variables only was poor with maximum cross-validated C-statistics of 0.613 and 0.574 among patients with index supply $\leq$30 days and $>$30 days, respectively. Using only indicators of adherence during the first 3 months of follow-up improved prediction accuracy substantially among patients with shorter initial dispensings (C = 0.828/0.524), and when combined with investigator-specified variables, prediction accuracy was further improved (C = 0.841/0.593).

Conclusions: Observed adherence immediately after initiation provided substantial information on future adherence behaviors for patients whose initial dispensings were relatively short. This approach may provide a simple algorithm for quickly identifying patients most likely to benefit from interventions to improve adherence.

376. Cost-related Medication Nonadherence among Medicare Beneficiaries Using Erythropoiesis-stimulating Agents

Minghui Li, Z Kevin Lu. *Department of Clinical Pharmacy and Outcomes Sciences, University of South Carolina, South Carolina College of Pharmacy, Columbia, SC, USA.*

Background: Use of erythropoiesis-stimulating agents (ESAs) poses a significant economic burden among Medicare beneficiaries. The burden of drug expenses, especially for the elderly and disabled, is one of the major reasons for nonadherence to prescription regimens.

Objectives: The objectives of this study were (1) to provide national estimates on the prevalence of cost-related medication nonadherence (CRN) to ESAs and (2) to identify predictors of CRN among Medicare beneficiaries using ESAs.

Methods: This study was a pooled cross-sectional study of the Medicare Current Beneficiary Survey from 2006 to 2010. The study sample was restricted to users of ESAs, defined as having at least one prescription of ESAs in Medicare Part B or D claims. Medicare beneficiaries who were institutionalized or were enrolled in health maintenance organization plans were excluded from the study. Self-reported CRN was the main outcome measure and was based on responses to five questions: taking smaller doses

of prescriptions, skipping doses to make prescriptions last longer, delaying obtaining prescriptions because of cost, deciding not to obtain prescriptions because of cost, and not obtaining prescriptions because it cost too much. Sampling weights were applied to obtain national estimates. Weighted logistic regression was conducted to identify predicators of CRN.

Results: Among 1098 person-years of Medicare beneficiaries using ESAs, 166 (15.40%, weighted percentage) reported experiencing CRN. Predictors of CRN identified in the study included using more than 30 prescriptions of ESAs (odds ratio [OR]: 2.50; 95% confidence interval [CI]: 1.23–5.07), being 65 to 74 years of age (OR: 3.56; 95%CI: 1.17–10.84), having a high school education (OR: 2.29; 95%CI: 1.10–4.76), having an annual income between $10 001 and $20 000 (OR: 1.76; 95%CI: 1.01–3.10), being disabled (OR: 7.51; 95%CI: 2.32–24.29), and having end-stage renal disease (OR: 3.14; 95%CI: 1.41–6.95).

Conclusions: Among Medicare beneficiaries, about one-seventh of users of ESAs reported nonadherence due to high drug costs. New strategies for better access to care are needed for patients with risks of nonadherence due to high medical costs.

377. Impact of Adherence to Antiosteoporotic Treatment on Recurrent Hip Fracture among a Population-based Cohort of Patients in Spain

Gabriel Sanfélix-Gimeno,[1,2] Julián Librero,[1,2] Isabel Hurtado,[1,2] Cristóbal Baixauli,[1,2] José Sanfélix-Genovés,[1,2,3] Salvador Peiró.[1,2] *[1]Health Services Research Unit, Center for Public Health Research (CSISP-FISABIO), Valencia, Spain; [2]Red de Investigación en Servicios de Salud en Enfermedades Crónicas, Valencia, Spain; [3]Fundación de Investigación del Hospital Clínico Universitario–Instituto de Investigación Sanitaria, Valencia, Spain.*

Background: Guidelines recommend pharmacologic treatment after hip fracture (HF) for secondary prevention of recurrent fractures. Treatment and adherence have been shown to be suboptimal and associated with higher incidence of recurrent HF. However, most studies have failed to account for competing risks of death, which are crucial in the elderly.

Objectives: The aim of this study was to estimate the impact of adherence to antiosteoporotic treatment on rehospitalization for HF.

Methods: Population-based retrospective cohort including all patients ≥65 years discharged alive after incident HF between 2008 and 2012 in Valencia region, Spain. Data were obtained by linking diverse electronic databases of the Valencia Health Department. Treatment was defined as having a prescription (filled or not) within 6 months after the index HF, and adherent was defined as having a proportion of days covered (PDC) ≥80%. Crude rates of recurrent HF and death were estimated. Survival analyses with and without adjustment for competing risk of death were used to estimate the risk of recurrent HF, adjusted by propensity scores and baseline covariates.

Results: We identified 19 405 patients discharged alive after HF (mean age: 83 years, 76% females). Seventy-two percent of patients were not treated, 20.3% were treated but non-adherent (PDC < 80), and 7.7% were adherent. Crude rates of recurrent HF were 25 per 1000 person-years for non-treated and non-adherent and 14 per 1000 person-years for adherent patients. Crude mortality rates per 1000 person-years were 22, 11, and 10 for non-treated, non-adherent, and adherent, respectively. The propensity score and baseline-covariates adjusted hazard ratio (HR) of a recurrent HF did not differ between untreated and non-adherent (HR:1.02; 95CI:0.87–1.21), whereas this was lower for adherent (HR:0.60; 95CI:0.44–0.81). Accounting for competing risk of death, the adjusted HR of recurrent HF was 1.18 (95CI:0.99–1.40) for non-adherent and 0.66 (95CI:0.49–0.90) for adherent, compared with non-treated.

Conclusions: Adherence to antiosteoporotic treatment for the secondary prevention of osteoporotic fracture was associated with reduced risk of recurrent HF, taking into account competing risk of death.

378. The Risk of Hypersensitivity Reactions among Older Rheumatoid Arthritis Patients on Biologics

Huifeng Yun,[1] Fenglong Xie,[2] Lang Chen,[2] James D Lewis,[3] Kenneth G Saag,[2] Jeffrey R Curtis.[2] *[1]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA; [3]Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA, USA.*

Background: Healthcare providers have been alerted to the potential drug hypersensitivity reactions (HSRs,

an uncommon adverse drug reaction but may be severe and result in mortality) in patients (pts) with RA, especially those receiving biologics. One case of a fatal HSR has been reported and associated with tocilizumab (TCZ).

Objectives: As the risks of HSRs by specific agent in RA pts are unclear, we compared drug-specific risks for HSR among Medicare RA pts.

Methods: Using Medicare data from 2006 to 2011 for 100% of pts with RA, we identified new users of infliximab (INF), abatacept (ABA), rituximab (RIT), TCZ and injected biologics (e.g. anti-TNF therapy). For each biologic administration (Adm), follow-up started on the date of drug Adm and ended at the earliest date of HSR, subsequent biologic Adm, death, coverage loss, 30-day follow-up period or 31 December 2011. We identified HSR using validated claims-based algorithms. We calculated the incidence rate (IR) of HSR for each biologic within 0–1, 2–14 and 15–30 days of Adm. Robust Poisson regression was used to compare the HSR risks across biologics adjusting for potential confounders. Sensitivity analysis was conducted using a nested case-crossover design to reduce within-person confounding.

Results: We identified 429 565 biologic Adms among 54 902 new biologic users. Of these, 29.9% were for ABA, 4.5% for RIT, 2.2% for TCZ, 23.2% for INF and 43.8% for injected biologics. Of 137 HSR cases we identified during follow-up, 77% occurred in an IP setting, 17.5% in ED and 5.5% in OTP. Sixty-four cases occurred within 1 day of biologic Adm. The IRs for HSR ranged from 3.0 to 337.2 per 1 000 000 person years across different biologics and timing of exposure. After adjustment, and using abatacept 15–30 days as the referent, ABA (7.1, 95%CI: 3.7, 13.8), INF (40.1, CI: 25.4, 63.2), RIT (38.3, CI: 20.2, 72.8) and TOC (28.5, CI: 13.2, 61.6) within 1 day of Adm were associated a significant higher risk of HSR. Sensitivity analysis yielded similar results.

Conclusions: Among RA pts taking biologics, infliximab, rituximab and tocilizumab were most strongly associated with HSRs within 1 day of Adm. The absolute IR of HSR events for all biologic exposures was low.

379. Tumor Necrosis Factor-α Inhibitor Use and the Risk of Incident Hypertension in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study

Rishi J Desai,[1] Daniel H Solomon,[1,2] Sebastian Schneeweiss,[1] Goodarz Danaei,[3] Katherine P Liao,[2] Seoyoung C Kim.[1,2] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA; [2]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, USA; [3]Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA.*

Background: Results from several small studies support the potential blood pressure lowering effect of tumor necrosis factor (TNF)-α inhibitors in rheumatoid arthritis (RA) patients. Yet, no study has compared the effect of TNF-α inhibitors with non-biologic disease-modifying anti-rheumatic drugs (nbDMARDs) on the development of incident hypertension in a population-based cohort of RA patients.

Objectives: The aim of this study was to compare the risk of incident hypertension between initiators of TNF-α inhibitors and initiators of nbDMARDs in a cohort of RA patients taking methotrexate monotherapy who are free from cardiovascular diseases or hypertension.

Methods: We conducted a cohort study using insurance claims data (2001–2012) from the USA. We identified initiators of either TNF-α inhibitors or nbDMARDs. Subsequent exposure to these agents was measured monthly in a time-varying manner. The outcome of interest was incident hypertension, defined by a diagnosis and a prescription for an antihypertensive drug. Marginal structural models (MSM) estimated hazard ratios (HR) that are adjusted for both baseline and time-varying confounders. To validate the primary analysis examining TNF-α inhibitors and hypertension association, we designed a verification analysis to evaluate a known association between leflunomide and hypertension using similar methodology.

Results: We identified 4822 initiations of TNF-α inhibitors and 2400 of nbDMARDs. Crude incidence rates of hypertension per 1000 person-years of follow-up were 36.1 (95%CI 31.8–40.7) for the TNF-α inhibitor group and 41.2 (95%CI 33.0–50.8) for the nbDMARDs. The crude HR of TNF-α inhibitors versus nbDMARDs for the risk of incident hypertension was 0.85 (95%CI 0.67–1.09). After adjusting for both baseline and time-varying covariates in MSM, the HR was 1.01 (95%CI 0.78–1.31). In the verification analysis, the adjusted HR of incident hypertension was 2.33 (95%CI 1.75–3.09) in leflunomide initiators compared with methotrexate initiators.

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Conclusions: Treatment with TNF-α inhibitors was not associated with a reduced risk of incident hypertension compared with nbDMARDs in RA patients.

380. The Risk of Hospitalized Infection Following Initiation of Biologic Agents versus Methotrexate in the Treatment of Juvennile Idiopathic Arthritis

Timothy Beukelman, Fenglong Xie, John Baddley, Lang Chen, Melissa Mannion, Kenneth G Saag, Jie Zhang, Jeffrey R Curtis. *University of Alabama at Birmingham, Birmingham, USA.*

Background: Biologic agents are highly effective for the treatment of juvenile idiopathic arthritis (JIA) but have the potential risk of increased serious infections.

Objectives: The aim of this study was to compare the rate of hospitalized infections among patients with JIA newly starting biologic agents versus newly starting methotrexate (MTX) without concurrent biologic use.

Methods: We used the national US Medicaid administrative claims from 2000 to 2010 inclusive. New users of the five available tumor necrosis factor inhibitors (TNFi), the interleukin 1 inhibitor anakinra (ANA), and MTX (without concurrent biologic use) were defined by a 6-month observable clean period of non-use. New users with a physician diagnosis code for JIA before age 16 years and prior to new use were included. Follow-up began on the day of the new use prescription fill. The outcome was hospital discharge with any infection as the primary diagnosis. Cox proportional hazards models were used to generate hazard ratios adjusted (aHR) for age, sex, race, systemic glucocorticoid (GC) use during the 60 days prior to the index date, comorbidities, and infections during the 6-month clean period. Among biologic users, use of MTX during follow-up was treated as a time-varying covariate.

Results: We identified 3075 new MTX users, 3471 new TNFi users, and 247 new ANA users. Crude infection rates per 100 person-years were MTX 4.7 (69/1478), TNFi 4.1 (86/2091), and ANA 15.2 (22/145). The aHR for TNFi versus MTX was 0.96 [0.61–1.5]. The aHR for ANA versus MTX was 2.3 [1.1–4.9]. Among all subjects in the study, baseline mean daily oral GC doses >10 mg or intravenous GC use was associated with increased infection risk (aHR 1.8 [1.1–2.7]). Among TNFi users, concurrent MTX was not associated with infection (aHR 1.2 [0.75–2.1]).

Conclusions: There was no increased risk of hospitalized infection among new TNFi users compared with new MTX users. New ANA users had an increased risk of infection that was numerically similar to the risk associated with high-dose GC use. ANA users very likely have systemic arthritis, which may confer a higher baseline risk of infection, but we could not readily assess this from our data.

381. Can Substituting a Biologics Offset the Risk of Serious Infection Associated with Glucocorticoids in RA Patients?

Huifeng Yun,[1] Lang Chen,[2] George Reed,[3] Joel M Kremer,[4] Jeffrey D Greenberg,[5] Jeffrey R Curtis.[2] *[1]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA; [3]University of Massachusetts Medical School, Worcester, MA, USA; [4]Albany Medical College, Albany, NY, USA; [5]New York University Hospital for Joint Diseases, New York, NY, USA.*

Background: Glucocorticoids (GCs) and biologic disease-modifying antirheumatic drugs (DMARDs) have previously been associated with serious infection events (SIEs) among rheumatoid arthritis (RA) patients.

Objectives: For patients on non-biologic DMARDs (nbDMARD) and GCs, we evaluated whether any increased risk for SIEs associated with adding a biologic might be offset if patients are able to reduce their GC exposure.

Methods: Using the 2002–2013 Corrona RA registry data, we identified eligible index visits where patients were on an nbDMARD and GCs, but not on biologics. We categorized time-varying exposure during follow-up into the following five categories: nbDMARDs + GC (prednisone <5 mg/day), nbDMARDs + GC (≥ 5 mg/day), biologic DMARD + GC (<5 mg/day), biologic DMARDs + GC (≥ 5 mg/day), and biologic DMARD without GCs. We calculated the incidence rate (IR) of SIEs for each exposure and compared risks using Cox regression adjusting for potential confounders among patients who were on nbDMARDs and GCs ≥ 5 mg/day at the start of follow-up.

Results: Of 7950 eligible index visits where patients initiated nbDMARDs and GCs, 25% were with GC <5 mg/day and 75% with GC ≥ 5 mg. For patients

who were treated with nbDMARDs and GCs <5 mg/day at the start of follow-up, 14.4% subsequently initiated biologics. For patients who were treated with nbDMARDs and ≥5 mg/day at the start of follow-up, 20% subsequently initiated biologics. Approximately 10–15% of patients, all who started on glucocorticoids, were able to discontinue them after adding biologics. Among patients who were on nbDMARDs and GCs ≥ 5 mg/day at the start of follow-up, we identified 204 SIEs yielding an IR for SIEs of 2.1 per 100 person years across all exposures. After adjustment and comparing with exposure of nbDMARDs + GCs (≥5 mg/day), patients on biologic DMARDs without steroid use were less likely to have an SIE (HR: 0.46; 95% CI: 0.24–0.88).

Conclusions: Many RA patients treated with nbDMARDs and glucocorticoids who initiate biologics are subsequently able to discontinue glucocorticoids. These individuals are at reduced risk for serious infections.

382. The Clinical and Economic Costs of Not Achieving Remission in Rheumatoid Arthritis

Jeffrey R Curtis, Lang Chen, Meredith Kilgore, Jeffrey D Greenberg, Huifeng Yun. *Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, USA; Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA; CORRONA, New York, NY, USA.*

Background: Treat to target guidelines recommends achieving a state of remission or low disease activity for rheumatoid arthritis (RA) patients. However, the benefit of lower disease activity for reduction of adverse events and costs is not clear.

Objectives: Our objective was to evaluate clinical outcomes and economic costs associated with RA disease activity.

Methods: We used CORRONA data linked to national Medicare data to identify RA patients and their disease activity, measured using the Clinical Disease Activity Index (CDAI) captured at each registry visit. CDAI was modeled using a time-varying area under the curve approach. Follow-up began at the date of the second registry visit, and the analysis was censored at time of the first event, 12/31/2012. Outcomes included all-cause hospitalization, a composite of hospitalization or ED visits, mortality, and paid monthly healthcare costs. Outcome-specific Cox proportional hazards models evaluated the adjusted hazard ratios (aHR) between disease activity and outcomes, controlling for potential confounders. Costs were analyzed with mixed models using a Gaussian distribution with log transformation.

Results: Depending on outcome, 4736 RA patients contributed up to 14 756 person years. Mean (SD) age was 69.8 (9.4) years, 75% women. At baseline, 59% of patients were in remission or low disease activity (LDA); 46% were on biologics. There was a strong dose–response relationship between the four categories of RA disease activity (remission, low, moderate, and high) and incidence rate for hospitalization (13.7, 19.2, 23.1, and 29.6 per 100 py). For hospitalization, all aHR were significant: 0.66 (remission), 0.88 (low), and 1.22 (high) referent to moderate. Similar crude and adjusted trends were observed for other outcomes. The crude difference in monthly costs between remission ($954/month) and moderate disease activity ($1620/month) was $666; the adjusted difference was −445.44 (−567.66, −323.23) per month.

Conclusions: Lower disease activity states in RA were associated with incrementally reduced risks of all-cause hospitalization, ED visits, mortality, and healthcare costs in a dose-dependent fashion.

383. Oral Glucocorticoid Use and Osteonecrosis in Chronic Inflammatory Diseases: A Population-based Cohort Study

Daniel B Horton,[1,2] Kevin Haynes,[1,3] Michelle R Denburg,[4] Mihir M Thacker,[5] Carlos D Rose,[2] Mary E Putt,[1] Brian L Strom.[1,6] *[1]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Wilmington, DE, USA; [3]Clinical Epidemiology, HealthCore, Wilmington, DE, USA; [4]Division of Nephrology, The Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [5]Department of Orthopedics, Nemours A.I. duPont Hospital for Children, Wilmington, DE, USA; [6]Rutgers Biomedical and Health Sciences, Rutgers University, Newark, NJ, USA.*

Background: Glucocorticoids have long been linked to the development of osteonecrosis, mostly in heavily exposed patients from specialty clinics.

Objectives: We tested the hypothesis that oral glucocorticoids were associated with osteonecrosis in children and adults with chronic inflammatory diseases in a dose-dependent relationship.

Methods: We performed a retrospective cohort study using The Health Improvement Network, a population-representative medical records database from the United Kingdom. The study population included people at least 2 years old diagnosed with asthma; inflammatory bowel disease (IBD); juvenile, psoriatic, or rheumatoid arthritis; psoriasis; or systemic lupus. Those with prevalent glucocorticoid use, prior osteonecrosis, malignancy, or other high-risk diseases were excluded. Prednisone-equivalent dose was classified in tertiles by age. The association between time-varying oral glucocorticoids and incident osteonecrosis was estimated using discrete time failure models. Hypothesis testing was one-sided, because glucocorticoids were unlikely to decrease the rate of osteonecrosis.

Results: There were 428 cases of osteonecrosis among 920 321 eligible subjects (incidence, age 2–17 years: 8.6 (95%CI 7.3, 10.3)/100 000 p-y; age ≥18 years: 5.6 (95%CI 5.1, 6.4)/100 000 p-y). After adjusting for age, sex, inflammatory disease, history of fracture, and number of drugs prescribed, any glucocorticoid exposure was most strongly associated with osteonecrosis among adults ages 18–49 years (adjusted HR 2.0, 90% CI 1.4, 2.8, $p < 0.001$). A dose response with cumulative glucocorticoid exposure was seen in adults (high versus low dose, ages 18–49 years: adjusted HR 3.2, 90% CI 1.6, 6.3, $p = 0.003$; ages ≥50 years: adjusted HR 1.6, 90% CI 1.01, 2.6, $p = 0.048$). Models examining maximum dose, dose * duration, and weight-based dosing were similar. No significant association was seen for children in any model. Arthritis, IBD, and lupus were independent risk factors, but disease did not modify the effects of glucocorticoid dose on osteonecrosis.

Conclusions: Glucocorticoids are associated with osteonecrosis in adults, most strongly in those under age 50 years, but not in children. Underlying disease does not modify this relationship.

384. Utilizing the PS to Estimate Treatment Effect in the Context of Many Covariates and Rare Outcome Events

Jessica M Franklin,[1] Wesley Eddings,[1] Peter Austin,[2] Elizabeth Stuart,[3] Robert Glynn,[1] Sebastian Schneeweiss.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.*

Background: Nonrandomized studies based on administrative healthcare data often use a propensity score (PS) to control hundreds of covariates. High-dimensional confounder control can lead to problems in causal inference due to inappropriate use of observations with extreme PS values. In studies with few outcome events, each observed event is highly influential, and potential problems are exacerbated.

Objectives: The aim of this study was to compare the performance of treatment effect estimation methods that utilize a PS in studies with many covariates and few outcome events.

Methods: We used an example study of the comparative effectiveness of oral anticoagulants for stroke prevention as the basis for a plasmode simulation study. We simulated 1000 datasets of 10 000 patients with an outcome risk of 2%, a true risk ratio (RR) treatment effect of 1.0, and confounding effects from 185 variables plus select interactions. In each dataset, we estimated PSs using several methods. We then estimated treatment effects from each PS model using various matching, stratification, regression, and weighting approaches.

Results: The crude RR estimate was biased (mean: 0.73 [IQR: 0.66–0.80]). Regression on the PS using flexible spline estimation and asymmetrical trimming at the 2.5% quantiles provided the best reduction in bias across varying PS models. A matching weight approach proposed by Li and Greene that mimics one-to-one matching but uses all patients also performed well if preceded by asymmetrical trimming. Ordinary one-to-one matching performed moderately well. In contrast, inverse probability of treatment weights (IPTW) performed poorly, except when preceded by trimming. For example, the mean RR when using a logistic PS model including all variables was 0.99 (0.85–1.10) for both regression on the PS and matching weights, versus 0.88 (0.65–0.94) for ordinary IPTW.

Conclusions: Methods that removed patients in areas of nonoverlap on the PS led to treatment effect estimates with the lowest bias, regardless of the PS model that was used. Approaches that did not account for PS

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nonoverlap did not effectively control bias. Additional simulations are needed to explore the performance of methods in other datasets.

385. Confounding Control Using Propensity Scores When the Exposure Is Infrequent: Making the Case for a Fine Stratification Approach

Rishi J Desai,[1] Kenneth J Rothman,[2,3] Brian T Bateman,[1] Sonia Hernandez-Diaz,[4] Krista F Huybrechts.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA; [2]Research Triangle Institute, Research Triangle Park, NC, USA; [3]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; [4]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: When exposure to medications is rare, propensity score matching (PSM) results in reduced precision because it discards a large proportion of unmatched unexposed patients. The relative performance of PS-stratification (PSS) in these circumstances is not well understood.

Objectives: Using both an empirical example of the fetal safety of statin use during pregnancy and simulations, we compared the performance of PSM and PSS in terms of confounding control and precision.

Methods: The association between first-trimester statin exposure (prevalence = 0.04%) and risk of malformations was evaluated in a cohort of 886 996 pregnant women. Three confounding-adjustment approaches were compared: (1) 1:1 PSM, (2) creating equally sized PS-strata ($n = 10\,50\,100$) after ranking the entire-cohort based on the PS, and (3) creating PS-strata ($n = 10\,50\,100$) after ranking only exposed based on the PS and assigning unexposed into these strata based on their PS. Relative risks were estimated using the Mantel–Haenszel pooling. The amount of confounding controlled was quantified, treating PSM as the reference. Precision was estimated using confidence limit ratios (CLR). To evaluate the performance of these methods under different scenarios, 100 cohorts of 100 000 were simulated with exposure prevalence 0.5% and 1% and a true null association. The overall accuracy of each method was assessed using mean squared error (MSE) in simulations.

Results: In the empirical example, entire-cohort PSS resulted in worse confounding control compared with exposed-only PSS (56% vs 96%, 81% vs 98%, and 88% vs 93% for 10, 50, and 100 strata). CLRs for the two PSS approaches were smaller (2.1) than for PSM (2.9). In the simulations, the exposed-only PSS resulted in the lowest MSEs, with a range over the scenarios from 0.01 to 0.03, compared with 0.03–0.08 for PSM, and 0.03–0.09 for whole-cohort PSS, using 10 or 50 strata. At 100 strata, MSEs from both PSS approaches were identical at 0.01.

Conclusions: Fine stratification, preferably based on exposed-only ranking if using fewer strata, may provide equivalent confounding control with greater precision compared with PSM when exposure is rare.

386. Comparing Three-way and Pairwise Propensity Score Matching Approaches for Analyses of a Real-world Comparative Effectiveness Study of Glaucoma Therapies (RiGOR)

Priscilla Velentgas,[1] Jaclyn LF Bosco,[1] Kristina Franke,[1] Anne L Coleman,[2] Flora C Lum,[3] Richard Gliklich,[4] Julie Park,[1] Zhaohui Su.[1] *[1]Real World and Late Phase Research, Quintiles, Cambridge, MA, USA; [2]Jules Stein Eye Institute, David Geffen School of Medicine and Fielding School of Public Health, University of California, Los Angeles, CA, USA; [3]H. Dunbar Hoskins, Jr. Center for Quality Eye Care, Foundation of the Academy of Ophthalmology, San Francisco, CA, USA; [4]Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA.*

Background: The three-way propensity score (PS) matching approach identifies which of the three treatments is best for a patient who could be considered for any of them, equivalent to requiring equipoise at baseline in a three-arm RCT. Previously, in simulated data and insurance claims, three-way matching compared with pairwise PS matching demonstrated similar covariate balance and effect estimates.

Objectives: The aim of this study was to compare the performance of three-way versus pairwise PS matching methods using data from a prospective observational CER study of three treatment modalities for glaucoma.

Methods: RiGOR, a prospective observational study conducted in US ophthalmology practices, compared the effectiveness of laser procedures, incisional surgery, and additional medication in lowering

intra-ocular pressure (IOP) by 15% at 12 months. Covariate balance and effect estimates of the three-way PS matching method developed by Rassen were compared with pairwise PS matching. The relative benefit of the treatment was estimated using conditional logistic regression.

Results: Balance on covariates was similar but somewhat greater for the pairwise matched groups than the three-way matched groups. The estimated associations between treatment type and 12-month success for the three-way matched and pairwise matched methods are as follows: three-way PS matched ($N = 164$ per group; laser versus additional medication OR 1.05, 95%CI 0.68–1.63; other surgery versus additional medication OR 3.20, 95%CI 1.97–5.18); pairwise PS matched (laser versus additional medication $n = 474$ per group, OR 1.05, 95% CI 0.82–1.35; and other surgery versus additional medication $n = 275$ per group, OR 2.97, 95%CI 2.00–4.41).

Conclusions: In this observational CER study, estimates of treatment benefit were fairly similar between the three-way and pairwise matching approaches. However, the number of patients dropped with three-way matching was higher given more stringent requirements of finding three equivalent patients for each match and was also limited by the n of the smallest treatment group resulting in wider confidence intervals.

387. The Choice of Analytic Strategies in Inverse-Probability-of-Treatment-Weighted Analysis: A Simulation Study

Shibing Yang,[1] Kate L Lapane,[2] Juan Lu,[1] Spencer Harpe,[4] Charles Eaton.[3] *[1]Virginia Commonwealth University, Richmond, VA, USA; [2]Quantitative Health Sciences, University of Massachusetts, Worcester, MA, USA; [3]Memorial Hospital of RI, Pawtucket, RI, USA; [4]Midwestern University, Chicago, IL, USA.*

Background: Inverse-probability-of-treatment-weighted estimation (IPTW) of marginal structural models relies on the correct estimation of the conditional probability of receiving observed treatment. Many studies applying IPTW have made an intention-to-treat (ITT) assumption. Invoking this assumption simplifies the weight construction process and the assumption of no uncontrolled confounding. However, violating the ITT assumption to some degree is common.

Objectives: The aim of this study was to explore the impact of ITT and complex treatment assignment assumptions made during weight construction on the validity and precision of estimates derived from inverse-probability-of-treatment-weighted analysis.

Methods: We simulated data assuming a non-experimental design that attempted to quantify the effect of statin on lowering low-density lipoprotein cholesterol (LDL-C). Overall, 324 scenarios were simulated with parameter values that varied on effect size, sample size, adherence level, probability of treatment initiation, and associations between LDL-C and treatment initiation and continuation. Simulated data were analyzed with four approaches: (1) IPTW assuming intention-to-treat; (2) IPTW assuming complex mechanisms of treatment assignment; (3) IPTW assuming a simple mechanism of treatment assignment; and (4) IPTW assuming invariant confounders.

Results: With a continuous outcome, estimates assuming intention-to-treat were biased toward the null when there was non-null treatment effect and non-adherence after treatment initiation. For each 1 percent decrease in treatment adherence, the bias in the average treatment effect increased by 1 percent. IPTW analyses that took into account the complex mechanisms of treatment assignment generated approximately unbiased estimates.

Conclusions: Studies performing intention-to-treat analyses should report adherence measures after treatment initiation so that findings can be interpreted under appropriate consideration of the observed adherence patterns. Studies attempting to estimate the actual effect of a time-varying treatment need to consider the complex mechanisms of treatment assignment during weight construction.

388. Finite-sample Performance of Inverse-probability Weighted Median Regression in the Presence of Large Weights

Maurice A Brookhart, Michele J Funk, Til Sturmer. *Department of Epidemiology, UNC Chapel Hill, Chapel Hill, NC, USA.*

Background: Large inverse-probability of treatment weights (IPTWs) often occur in pharmacoepidemiologic research and can result in inefficient estimators of treatment effects that can also possess some amount of finite-sample bias.

Objectives: We sought to determine whether IPTW estimators of the effect of treatment on medians would be less sensitive to large weights than IPTW estimators of effect of treatment on means.

Methods: We simulated the full counterfactual data under various data-generating mechanisms in which we varied the sample size ($n = 100$, 500, and 5000) and the strength of the effect of the exposure on the outcome. For each parameter combination, we simulated 5000 datasets. Within each dataset, we evaluated stabilized IPTW mean regression, IPTW median regression with normalized weights, augmented IPTW mean regression (a "doubly robust" estimator that depends on both models for an outcome and treatment), and a benchmark maximum likelihood estimator. All models used a correct specification of the propensity score model, and the augmented IPTW estimator used both a correct treatment and an outcome model specification, thus achieving semiparametric efficiency.

Results: In small sample sizes with large weights, we found that the IPTW median estimator always had less bias than the IPTW mean estimator but greater variance, resulting in a mean squared error that was 43%, 38%, and 32% higher on relative scale, for $n = 100$, 500, and 5000, respectively. The augmented IPTW mean estimator was effectively unbiased with an estimated percentage bias never more than 4% across all scenarios. It also was more efficient than both of the standard IPTW estimators for $n = 500$ and 5000. The MLE was the least biased and most efficient across all scenarios.

Conclusions: IPTW median regression was less biased but substantially less efficient than IPTW mean regression in all scenarios considered. The augmented IPTW mean estimator exhibited better performance than either the IPTW mean or median estimator for moderate sample sizes.

389. Performance of the High-dimensional Propensity Score in Adjusting for Hidden Measured Confounders

Jason R Guertin,[1,2] Elham Rahme,[3] Jacques LeLorier.[1]
[1]*Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada;* [2]*PATH Research Institute, Hamilton, ON, Canada;* [3]*Research Institute of the McGill University Health Centre, Montreal, QC, Canada.*

Background: High-dimensional propensity scores (hdPS) can adjust for measured confounders, but it remains unclear if they can adjust for unmeasured confounders. Internal validation studies may be used to gather additional information on unmeasured confounders, but patient confidentiality policy may greatly limit their feasibility. Measured confounders that are hidden to the hdPS algorithm and not subsequently adjusted for within multivariable regression models (hereby, defined as hidden confounders) should be similar to unmeasured confounders.

Objectives: Our goal was to identify if the hdPS method could adjust for hidden confounders of the association between the exposure to high versus low-dose statins and the risk of diabetes.

Methods: A cohort of diabetes-free incident users of statins was provided to us from the Quebec publicly funded medico-administrative databases (full cohort). The hdPS algorithm was used to estimate two hdPS: the first version (hdPS-1) was estimated using data provided by six data dimensions, and the second version (hdPS-2) was estimated using data provided from only two of the six data dimensions. Two matched sub-cohorts were created by matching one patient initiated on a high-dose statin to one patient initiated on a low-dose statin based on either hdPS-1 (matched hdPS full info sub-cohort) or hdPS-2 (matched hdPS hidden info sub-cohort). Performance of hdPS-1 and hdPS-2 was compared by means of the standardized differences (SDD) regarding 19 characteristics (data on eight of the 19 characteristics were hidden to the hdPS algorithm when estimating the hdPS-2).

Results: Eight out of the 19 characteristics were shown to be unbalanced within the full cohort. Matching on either hdPS achieved balance on all 19 characteristics (i.e., SDD within both sub-cohorts were all <0.1). Greater balance between patient sub-groups (i.e., lower SDD) was obtained within the matched hdPS full info sub-cohort than within the matched hdPS hidden info sub-cohort for 16 out of the 19 characteristics.

Conclusions: Our results indicate that the hdPS method was able to adjust for hidden confounders supporting the claim that the hdPS method can adjust for at least some unmeasured confounders.

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390. The Current State of Pharmacovigilance in African Countries

Danya M Qato,[1] Mariam Squalli,[2] Souad Skalli,[2] Rachida Soulaymani.[2] *[1]Health Services, Policy & Practice, Brown University School of Public Health, Providence, RI, USA; [2]Centre Anti Poison et de Pharmacovigilance du Maroc, World Health Organization Collaborating Centre for Pharmacovigilance, Rabat, Morocco.*

Background: Although the urgency of strengthening pharmacovigilance in developing health systems is increasingly being recognized, little is known about pharmacovigilance programs in African countries. This study is the first transnational comparative study to evaluate and quantify the pharmacovigilance situation in the continent.

Objectives: The objectives of this study were to describe, quantify, and evaluate the pharmacovigilance situation in African countries.

Methods: A standardized questionnaire, adapted from the Indicator-based Pharmacovigilance Assessment Tool (IPAT), was carried out between 1 May and 31 August 2013. It was designed to collect information on the structures, processes, and impact of pharmacovigilance activities and was distributed via e-mail to pharmacovigilance contact persons or appropriate Ministry of Health representatives.

Results: Eighty percent of respondents answered the questionnaire representing 32 African countries. Key findings included 31 countries (97%) have a national center or pharmacovigilance unit; 75% ($n=24$) of countries have a national policy, regulation, or legislation for pharmacovigilance activities; and 25% ($n=8$) of countries still have not implemented any form of regulation. Fifteen countries (47%) confirmed the presence of a budget for pharmacovigilance activities. Seventy-five percent ($n=24$) of responding countries have staff working full time to undertake pharmacovigilance activities, 31% ($n=10$) of countries have never sent any individual case safety reports to the Uppsala Monitoring Centre, and 62% ($n=20$) use VigiFlow® technology. The mean total performance score obtained by respondent countries was 19 ± 7 from a total possible best performance score of 32 (with a range from 2 to 29). This score comprises structural, process, and impact indicator assessments on which countries scored on average 12 ± 4 (from a total possible score of 16 with a range from 2 to 16), 4 ± 3 (from a total possible score of 9 with a range from 0 to 8), and 3 ± 2 (from a total possible score of 7 with a range from 0 to 7), respectively.

Conclusions: There is profound heterogeneity in the strength of pharmacovigilance programs between African countries, and efforts to bridge the gap in drug safety systems development should be amplified.

391. Medication Discussions on Social Media—What Are People Talking About?

Michele Thomas,[2] Bradley Turnbull,[3] Jeffery L Painter,[1] Rachael L DiSantostefano,[1] Greg Powell.[1] *[1]GlaxoSmithKline, RTP, NC, USA; [2]Blue Zone Industries, Inc., Chester Springs, PA, USA; [3]Department of Statistics, North Carolina State University, Raleigh, NC, USA.*

Background: Patients and caregivers use social media to share health and medication information. The extent to which these posts discuss safety, benefits, or other information has not been fully explored.

Objectives: The aim of this study was to describe safety and non-safety discussion topics in social media among individuals communicating about 15 GSK medicines on Twitter and Facebook.

Methods: From a 1-year period (1 September 2013–31 August 2014), social media posts (94% Twitter, 6% Facebook) containing 15 GSK medications were extracted. De-identified posts were categorized as containing language resembling potential adverse events (ProtoAEs) or Mentions (i.e., not ProtoAEs) using proprietary natural language processing from MedWatcher Social™. All ProtoAEs and a 10% stratified random sample of Mentions were manually reviewed by healthcare professionals for available demographics and safety information. Using R, Mentions were "clustered" by applying the k-means clustering algorithm to a weighted document-term matrix, which characterizes the frequency of terms within each Mention. Themes for medications of interest were examined by subgroups to identify potential differences, and time trends were also examined.

Results: Of the total posts (9839) obtained for the 15 GSK medicines, 7344 posts (74.6%) contained mention of at least one medicine (Mentions). Forty-five

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percent of Mentions were posted by patients, 39.9% had poster undetermined, and 15.6% were not the patient. We identified a graphical method and representative posts for reviewing clusters of social media medication discussions to identify themes pertinent to safety and other topics of interest. Most Twitter medication discussion clusters had notable time-based peaks (71%), and less than half of representative posts contained indication (43%). Patients' Twitter discussion themes centered on lack of efficacy (47%), medication benefits (35%), product complaints (12%), and dosing-related topics (6%).

Conclusions: In this 1-year study of social media medication posts, we were able to distinguish themes among products and changes over time. More research is needed to understand the utility of theme analysis for safety surveillance.

392. Essure Problems: Utilizing Facebook and Mobile Apps in Pharmacovigilance

Chi Y Bahk,[1] Melanie Goshgarian,[2] Krystal Donahue,[2] Clark C Freifeld,[1] Christopher Menone,[1] Carrie Pierce,[1] Harold Rodriguez,[1] John S Brownstein,[1] Nabarun Dasgupta.[1] *[1]Epidemico Inc, Boston, MA, USA; [2]"Essure Problems" Facebook Group, Boston, MA, USA.*

Background: Submitting a voluntary adverse event (AE) report to FDA takes 40 minutes. Mobile apps and social media outreach may increase efficiency. In 2011, the Center for Devices and Radiologic Health (CDRH) launched a free, public mobile app for AE reporting. In 2013, a Facebook patient community adopted the app for reporting on a hysteroscopic sterilization device: Essure.

Objectives: The aim of this study was to analyze effect of using a mobile app and social media outreach in AE reporting.

Methods: Patient community outreach was conducted to administrators of the Facebook group "Essure Problems" (~15 000 members) to gather individual case safety reports (ICSR). Semi-structured fields in the app mirrored parts of MedWatch 3500 Form. ICSRs were transmitted to CDRH via electronic gateway, and anonymized versions were posted in the app. Public reports received through the app from 11 May 2013 to 7 December 2014 were coded (MedDRA v17) and analyzed for descriptive metrics including VigiGrade completeness scores.

Results: The average Essure report took 8.5 minutes to complete. Submissions from 1349 women, average age 34 years, were analyzed. Serious outcomes, including hospitalization, disability, and permanent damage, were reported by 1047 (77.6%) women; 13 135 product–event pairs were reported (327 unique preferred terms), most frequently: fatigue ($n = 491$), back pain (468), pelvic pain (459), and abdominal pain (430). Important Medical Events, including mental impairment (148), device dislocation (111), salpingectomy (64), and post-procedural hemorrhage (45), were reported by 598 (44.3%) women. Other events of interest included alopecia ($n = 252$) and allergy to metals (109), primarily nickel. VigiGrade completeness scores were high (0.80 $\pm$ 0.15%) with time-to-onset information in 63.6% of submissions.

Conclusions: Outreach via an online patient community, coupled with an easy-to-use mobile app, allowed rapid and detailed ICSRs to be submitted, with gains in efficiency. Two-way communication and public posting of narratives led to successful engagement within a motivation–incentive–activation–behavior framework. Further research is needed to understand how biases operate differently from those of traditional pharmacovigilance.

393. Does Direct-to-consumer Advertising Lead to Stimulated Reporting of Adverse Events in Social Media?

Nabarun Dasgupta, Carrie Pierce, Eric Xu, Christopher M Menone, Clark F Freifeld, Harold Rodriguez, Robin Heffernan, Chi Bahk, John S Brownstein. *Epidemico, Inc., Boston, MA, USA.*

Background: Many patients do not report adverse events to regulatory agencies or manufacturers because they are unaware that they can or should. However, patients often discuss AEs in social media. Methodological studies are needed in the nascent field of social listening for pharmacovigilance to understand reporting biases.

Objectives: The objectives of this study were to determine if rates of AEs are higher with approved direct-to-consumer advertising and to determine time-of-day patterns associated with social media AEs.

Methods: A natural language processing algorithm was used to detect adverse events in public initial posts

from Twitter and Facebook. A vernacular-to-MedDRA dictionary was used to code preferred terms. A Bayesian machine learning algorithm was applied to remove spam and identify English language posts with resemblance to AEs (Proto-AEs) in an automated manner. Sixty drugs with approved US DTC advertising were analyzed and compared with 60 common prescription drugs, from September 2013 through January 2015. Multiple posts were consolidated. Time series analyses will be presented showing time-of-day effects. Results will be updated through mid-August 2015; the pool of non-DTC drugs will be expanded.

Results: There were 1 881 714 mentions for 60 DTC drugs in Facebook and Twitter. After removing spam, there were 435 460 filtered mentions and 23 892 Proto-AEs. For non-DTC drugs, there were 1 587 197 mentions, 724 042 filtered mentions, and 26 048 Proto-AEs. DTC drugs had a Proto-AE proportion of 5.5% (95%CI: 4.3, 6.7), while non-DTC drugs had 3.6% (95%CI: 2.3%, 4.9%). Chantix ($n = 5420$), Lyrica ($n = 4157$), and Cymbalta ($n = 3241$) had the highest numbers of Proto-AEs. Copaxone (22.5%), Daliresp (14.3%), and Humira (12.2%) had the highest proportions. Distinct patterns of filtered mentions were evident for television ads during afternoon soap operas (e.g., OxyTrol) versus prime time (e.g., Eliquis), with some temporally associated increase in AEs.

Conclusions: We found evidence that DTC drugs may have elevated Proto-AEs in social media. There were spikes in mentions immediately after airing of TV ads. More methodological research is warranted to understand the mechanisms of bias in social listening for pharmacovigilance.

394. Association between Oral Fluoroquinolone Use and Retinal Detachment: A Self-controlled Case Series Study

Fanny Raguideau,[1] Magali Lemaitre,[1] Mahmoud Zureik.[1] *[1]Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Saint Denis, France; [2]Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Saint Denis, France; [3]Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), France, Saint Denis, France.*

Background: Several studies focused on the impact of current oral fluoroquinolone use on the risk of retinal detachment, but the existence of this association is under debate. Because of the widespread fluoroquinolone use in France, it has become necessary to study this association using the main French administrative claim database.

Objectives: The aim of this study was to investigate the association between oral fluoroquinolone use and the risk of retinal detachment.

Methods: A self-controlled case series study was conducted using the French national health insurance database (SNIIRAM) linked to the French hospital discharge database (PMSI). From 1 July 2010 through 31 December 2013, 27 871 adult patients with retinal detachment and who comply with the selection criteria were included in our study.

The risk of retinal detachment occurring in either of the 0- to 10-day (current use), 11- to 30-day (recent use), and 31- to 60-day (past use) risk periods was compared with the risk in the 61- to 180-day reference period. The association with current fluoroquinolone use was also assessed by the type of fluoroquinolone.

Results: A total of 1222 cases exposed to fluoroquinolone during the observation period were studied corresponding to 96, 119, 196, and 811 cases during the 0- to 10-day, 11-to 30-day, 31- to 60-day risk periods, and the reference period, respectively. Current fluoroquinolone use was significantly associated with a higher risk of developing a retinal detachment (adjusted incidence risk ratio [IRR], 1.46 [95%CI, 1.17–1.81]). Neither recent use (IRR, 0.94 [95%CI, 0.78–1.14]) nor past use (IRR, 1.06 [95%CI, 0.91–1.24]) was associated with a retinal detachment. Current levofloxacin use was significantly associated with a higher risk of retinal detachment (IRR, 1.98 [95%CI, 1.26–3.07]). Other fluoroquinolones showed a positive but non-significant association.

Conclusions: Current oral fluoroquinolone use was associated with a significant increased risk of retinal detachment in our study. These results should be taken into account in the management of patients requiring treatment with this antibiotic class.

395. A Quality-weighted Prospective Meta-analysis for Integrating Evidence from Multiple Data Streams

Grace Wangge,[1,2] Sebastian Schneeweiss,[1] Joshua J Gagne.[1] *[1]Division of Pharmacoepidemiology and*

Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA; [2]Division of Epidemiology and Statistics, Department of Community Medicine, Universitas Indonesia, Jakarta, DKI Jakarta, Indonesia.

Background: Decisions related to drug safety often involve information from randomized controlled trials (RCTs), observational studies, and case reports. They are usually incorporated into a subjective decision analytic framework.

Objectives: The aim of this study was to develop an approach to support safety decision-making that quantitatively integrates data from multiple sources as the data procure over a drug's life cycle.

Methods: We developed a quality-weighted prospective meta-analysis that uses cumulative meta-analysis to integrate information from multiple data sources and gives preference to certain information using quality-weighted random effects analyses. We applied it to two cases: telithromycin (approved April 2004) and hepatotoxicity, and rofecoxib (approved May 1999) and myocardial infarction (MI). We emulated continuous safety monitoring by incorporating data from RCTs, observational studies, and individual cases reported to FDA's Adverse Event Reporting System (FAERS) as these data became available. We determined when the approach generated a safety alert for each case.

Results: In the telithromycin case study, we included data from 12 RCTs, three cohort studies, and an analysis of FAERS data. The 95% confidence interval (CI) of the cumulative relative event ratio (RER) excluded one in the second quarter of 2005 (RER, 1.60; 95% CI, 1.08–2.28). In the second quarter of 2006, when telithromycin's label was changed to include a bolded warning about hepatotoxicity, the cumulative RER was 1.77 (95%CI, 1.17–2.68). We included seven RCTs, 17 observational studies, and an analysis of FAERS data in the second case study. The 95%CI of the cumulative RER for MI excluded one in the second quarter of 2000. When rofecoxib was voluntarily withdrawn in 2004, the cumulative RER was 1.22 (95%CI, 1.12–1.59).

Conclusions: We developed an approach that can be used to combine and quality-weight data from multiple sources prospectively. Had the approach been applied to telithromycin, it would have indicated an alert for hepatotoxicity a year before a bolded warning was added to its label. Had it been applied to rofecoxib, it would have indicated an alert more than 2 years before the drug was withdrawn.

396. Prognostic Factors for Gastric Cancer after Surgical Resection—A Retrospective Study for 1766 Patients in Shanghai

Shen Zhenbin,[1] Wang Cong,[1] Luo Jianfeng,[2] Zhao Naiqing,[2] Liu Fenglin,[1] Shen Kuntang,[1] Wang Lisa,[3] Chu Laura,[3] Li Yunlin,[4] Piao Yongzhe,[4] Sun Qiao,[4] Xiao Yan,[4] Sun Yihong.[1] *[1]Department of General Surgery, Zhongshan Hospital, Shanghai, China; [2]Department of Biostatistics, School of Public Health, Fudan University, Shanghai, China; [3]Genentech, Inc., South San Francisco, CA, USA; [4]Roche Product Development in Asia Pacific, Shanghai, China.*

Background: Gastric cancer (GC) is the third cause of cancer death in Shanghai, China, but the overall treatment response is poor. Data on prognostic factor and survival are limited.

Objectives: This study aimed to describe overall survival and identify prognostic factors for survival among GC patients (pts) after radical resection.

Methods: The clinical data of 1766 GC patients who are Shanghai residents and who had undergone resection in Zhongshan hospital in Shanghai from 2003 to 2011 were retrospectively reviewed and analyzed. Radical surgery was performed for 1605 pts when possible. Demographic, tumor characteristics, treatments, and overall survival data were collected. Survival was calculated by the Kaplan–Meier method, and log-rank test was used to determine significance. Prognostic factors were analyzed using Cox regression multivariate analysis.

Results: The 25 percentile survival time for all patients was 19.2 months. The 25 percentile survival time by pTNM stage Tis, II, III, and IV disease were 70.0, 52.8,13.2, and 10.1 months, respectively. In univariate analyses, gender and adjuvant chemotherapy (yes/no) were not statistically related to survival ($p > 0.05$). However, age, surgery type, tumor differentiation, tumor location, macroscopic types, histological type, lymphatic/venous invasion, depth of infiltration, presence of lymph node metastasis, presence of distant metastasis, and number of lymph node removed were significantly related to survival

($p < 0.05$). In multivariate Cox regression model analysis, all the aforementioned factors that are found significant in the univariate analysis, except for histological type and surgery type, were also statistically significant prognostic factors.

Conclusions: Age, tumor differentiation, tumor location, macroscopic types, lymphatic/venous invasion, depth of infiltration, presence of lymph node metastasis, and presence of distant metastasis were independent prognostic factors for survival among radical resected GC patients. Extensive lymph nodes dissection was the most important treatment. GC remains a significant medical need in China, and effective therapies are urgently needed in late-stage patients.

397. Prognosis of Patients with Acute Lymphoblastic Leukemia

Thomas B Rasmussen,[1] Alma B Pedersen,[1] Sally Wetten,[2] Aaron J Katz,[3] Michael A Kelsh,[3] Victoria M Chia,[3] Mette Norgaard.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Centre for Observational Research, Amgen Ltd, Uxbridge, UK; [3]Center for Observational Research, Amgen Inc, Thousand Oaks, CA, USA.*

Background: Acute lymphocytic leukemia (ALL) is a rare cancer with an incidence of one case per 100 000 person-years. Still, ALL accounts for 20% of all cancers among persons younger than 20 years of age and is the most common cancer in children. However, the prognosis varies greatly by age.

Objectives: The aim of this study was to estimate complete remission (CR), stem cell transplantation (SCT), and survival in ALL patients stratified by age, using linked population-based registries (Cancer Registry, National Registry of Patients, Civil Registration System, and National Pathology Registry) in Denmark (~5.6 million citizens).

Methods: We included all patients diagnosed with ALL from 1998 to 2010. We calculated the proportion of patients achieving CR within 3 years of diagnosis and the probability of receiving SCT within 5 years of diagnosis. To estimate survival, we used the Kaplan–Meier curves. Cox regression was used to estimate hazard ratios (aHR) with 95%CI for overall mortality within 5 years of diagnosis, adjusting for sex, comorbidity, and phenotype.

Results: Among 805 patients (61% were 0–15 years of age at the time of diagnosis), 91.3% (CI: 89.2–93.1) achieved CR. For patients older than 60 years, CR was 53.9% (CI: 44.8–62.8) compared with 94.5% (CI: 90.6–97.0) for patients aged 16–59 years and 98.8% (CI: 97.5–99.5) for patients aged 0–15 years. The proportion of patients receiving an SCT was 17%, with 1.2% (CI: 0.1–5.9), 38% (CI: 29.9–45.9), and 12.7% (CI: 9.4–16.4) among patients older than 60 years, 16–59 years and 0–15 years of age, respectively. Overall, 5-year survival was 67.5% (CI: 64.0–70.6). For patients older than 60 years, survival was 10.6% (CI: 5.7–17.2) compared with 48.7% (CI: 41.3–55.7) for patients aged 16–59 years (aHR 0.31, CI: 0.23–0.42) and 88.1% (CI: 84.9–90.7) for patients aged 0–15 years (aHR 0.06, CI: 0.04–0.08).

Conclusions: CR and survival following ALL was substantially higher in children and patients younger than 60 years of age at the time of diagnosis than in patients older than 60 years.

398. Comparative Effectiveness of Chemotherapy versus Resection of the Primary Tumor as the Initial Treatment Modality in Older Patients with Stage IV Colorectal Cancer

Hemalkumar B Mehta,[1] Gabriela M Vargas,[2] Nina P Tamirisa,[1,3] Deepak Adhikari,[1] Kimberly M Brown,[1] Taylor S Riall.[1] *[1]Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA; [2]Louisiana State University-Shreveport, Shreveport, LA, USA; [3]University of California, San Francisco-East Bay, Oakland, CA, USA.*

Background: With the increased effectiveness of modern chemotherapy, the use of chemotherapy or resection of the primary tumor (surgery) as the initial treatment modality for stage IV colorectal cancer (CRC) is controversial.

Objectives: The aim of this study was to determine the comparative effectiveness of chemotherapy versus surgery as the initial treatment modality on survival in patients presenting with stage IV CRC.

Methods: This retrospective cohort study included elderly patients presenting with stage IV CRC identified in the Surveillance, Epidemiology, and End Results, Texas Cancer Registry, and linked Medicare claims data (2000–2009). The main exposure was the use of

chemotherapy or surgery as the initial treatment modality, regardless of receipt of the second modality. The association of exposure with 2-year survival was estimated using multivariable Cox proportional hazards models, propensity score (PS), and instrumental variable analyses. Percentage of use of chemotherapy as initial treatment by health services area was used as the instrumental variable.

Results: Of 7425 patients presenting with stage IV CRC, 28.8% received chemotherapy and 71.2% received surgery as the initial treatment. In a Cox proportional hazards model adjusted for potential confounders, chemotherapy versus surgery as the initial treatment was associated with improved survival (HR, 0.86; 95%CI, 0.81–0.92), regardless of subsequent receipt of treatment. The results were similar using PS methods: PS regression adjustment (HR, 0.85; 95%CI, 0.79–0.91), PS inverse probability of treatment weighting (HR, 0.83; 95%CI, 0.78–0.88), and PS matching (HR, 0.85; 95%CI, 0.79–0.93). The instrumental variable analysis showed no association between chemotherapy and surgery as the initial treatment and survival (HR, 0.99; 95%CI, 0.67–1.44).

Conclusions: Instrumental variable analysis, which controls for measured and unmeasured confounders, showed no difference between chemotherapy and surgery as the initial treatment modality for survival in stage IV CRC patients. Use of a chemotherapy first-approach may maximize chemotherapy rates and minimize surgical morbidity.

399. Effect of Chemotherapy on Chronic Comorbid Conditions in Elderly Breast Cancer Patients

Kitaw Demissie,[1,2,5] Joel Swerdel,[1] Tobias Gerhard.[1,3,4]
[1]Rutgers Pharmacoepidemiology Program, Rutgers University, New Brunswick, NJ, USA; [2]Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA; [3]Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Piscataway, NJ, USA; [4]Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA; [5]Cancer Prevention and Control, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA.

Background: Prior studies have indicated an increase in the incidence of new comorbid conditions following breast cancer diagnosis. The role of chemotherapy in that finding was unclear.

Objectives: The aim of this study was to examine the association between breast cancer chemotherapy treatment and the development of new comorbid conditions in the first 2 years following treatment.

Methods: The Surveillance, Epidemiology, and End Results-linked Medicare data from 1992 to 2010 were used. Elderly women diagnosed with Stages I–III breast cancer were included. We used inpatient and outpatient diagnoses prior to breast cancer treatment to determine those at risk for developing new comorbid conditions following breast cancer treatment. Patients with a history of a particular illness prior to breast cancer were excluded from analysis for that illness after breast cancer treatment. Diagnosis codes were used to determine the presence of diabetes, hypertension, arthritis, osteoporosis, emphysema, chronic and acute gall bladder disease, chronic non-alcoholic liver disease, chronic kidney disease, heart failure, deep vein thrombosis, pulmonary embolism, hypothyroidism, stoke, and myocardial infarction. The 1- and 2-year incidence rates of new comorbid conditions in patients who received chemotherapy ($N = 2414$) were compared with patients with surgery only ($N = 12\,107$).

Results: After accounting for important confounders, a significant increase was observed in the 1-year development of osteoporosis [relative risk (RR) = 1.59, 95% confidence interval (CI): 1.43, 1.77], chronic and acute gall bladder disease (RR: 1.65, 95%CI: 1.16, 2.36), chronic renal disease (RR:1.34, 95%CI: 1.05, 1.70), heart failure (RR: 1.65, 95%CI: 1.37, 1.99), deep vein thrombosis (RR: 2.88, 95%CI: 2.32, 3.57), and pulmonary embolism (RR: 2.29, 95%CI: 1.62, 3.23) in women with early stage breast cancer who received chemotherapy as compared with those who did not. We also found significant increases in the 2-year development of hypothyroidism (RR: 1.31, 95%CI: 1.09, 1.56).

Conclusions: Oncologists treating breast cancer patients should be alert in the identification of new comorbid conditions and referring their patients to appropriate specialty care.

400. The Effect of Chemotherapy-induced Anemia on the Risk of Dose Delay and Dose Reduction

Leila Family,[1] Chun Chao,[1] Lanfang Xu,[1] Kimberly Cannavale,[1] Olivia Sattayapiwat,[1] Roberto

Rodriguez,[2] John H Page,[3] Hairong Xu.[3] *[1]Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA; [2]Los Angeles Medical Center, Kaiser Permanente Southern California, Los Angeles, CA, USA; [3]Amgen, Inc, Thousand Oaks, CA, USA.*

Background: Myelosuppression is a major dose-limiting toxicity associated with chemotherapy. While chemotherapy-induced neutropenia has been shown to be associated with dose delay and dose reduction, the effect of anemia is less known.

Objectives: The current study aims to evaluate moderate and severe anemia as potential risk factors for dose delay and dose reduction in the first course of chemotherapy.

Methods: We identified a cohort of Kaiser Permanente patients diagnosed with incident non-Hodgkin's lymphoma (NHL), breast, lung, gastric, ovarian, or colorectal cancers between 2010 and 2012, with at least one hemoglobin measurement during the first course of chemotherapy. Generalized linear mixed effects models were used to study the effect of anemia (grades 2 and 3–4 vs. grade 1/none) on subsequent chemotherapy dose delay/dose reduction, adjusting for age, sex, race/ethnicity, stage, cycle, comorbidities, liver function test, kidney function test, platelet count, absolute neutrophil count, and febrile neutropenia. Dose delay was defined as $\geq$3 day from the expected administration of a given cycle. Dose reduction was defined as a >15% decrease for one or more myelosuppressive agents in a cycle.

Results: Our study included 574 NHL, 2043 breast, 463 lung, 113 gastric, 558 colorectal, 204 ovarian, and 558 colorectal cancer patients. After adjusting for potential confounders, anemia was significantly associated with subsequent dose delay and dose reduction overall ($OR_{\text{grade 2 anemia}} = 1.46$, 95%CI: 1.32, 1.62 and $OR_{\text{grade 3–4 anemia}} = 2.02$, 95%CI: 1.41, 2.89). This association was stronger in stage IV cancer compared with stages I–III cancer ($OR_{\text{Stage I–III}} = 1.33$, 95%CI: 1.18, 1.49 vs. $OR_{\text{stage IV}} = 1.94$, 95%CI: 1.58, 2.38) for grade 2 anemia and ($OR_{\text{Stage I–III}} = 1.81$, 95% CI: 1.18, 2.76 and $OR_{\text{StageIV}} = 2.83$, 95%CI: 1.42, 5.62) for grades 3–4 anemia. Stratified by cancer type, this association was observed in all cancer types except NHL.

Conclusions: We found that the occurrence of grade 2 + anemia increased the risk of having a dose delay and/or dose reduction in the subsequent chemotherapy cycle. This may, in part, explain the link between the occurrence of anemia and inferior patient outcomes.

401. Risk of Wernicke's Encephalopathy in Patients with Myeloproliferative Neoplasm

Jasmanda H Wu, Ling Zhang, Stephen Lin, Juhaeri Juhaeri.*Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, USA.*

Background: Wernicke's encephalopathy (WE) is an acute neuropsychiatric syndrome resulting from thiamine deficiency. This neurological deterioration is potentially debilitating or fatal. Cancer patients are at high risk of WE because of chronic malnutrition, chemotherapy-induced nausea and vomiting, and consumption of thiamine by rapidly growing tumors. Very little published research addresses the risk of WE in patients with myeloproliferative neoplasm (MPN).

Objectives: The objectives of this study were to estimate the incidence of WE among patients with MPN and to compare it with those without MPN.

Methods: Patients with a diagnosis of MPN, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), were identified from 1 January 2003 to 31 March 2013 using the US MarketScan database. The control cohort consisted of a random sample matched to the MPN cohort by age and gender in a 1:1 ratio. Diagnosis of WE was ascertained using ICD-9-CM 265.0, 265.1, 291.1, 294.0, or J code J3411. The two study cohorts were followed for WE from the index date. Cox proportional hazards modeling was used to compare the rates between two cohorts and control for confounding variables.

Results: A total of 39 761 MPN patients, including PV (51%), ET (42%), post-PV MF (0.2%), post-ET MF (1%), and PMF (2.8%), were identified. Approximately 27% of them were >65 years of age, and 51% were male. Patients with MPN had higher rates of WE, compared with those without MPN (MPN vs. non-MPN: 1.09 vs. 0.39/1000 person-year, hazard ratio = 2.19, 95% confidence interval: 1.43–3.34). The incidence rate of WE was higher in males (male vs. female: 0.93 vs. 0.55/1000 person-year). No specific pattern was observed in age subgroups for both cohorts (e.g., MPN: age <18 vs. 18–39 vs. 40–49 vs.

50–59 vs. 60–69 vs. >70 years = 0 vs. 0.85 vs. 1.09 vs. 1.16 vs. 0.72 vs. 0.86/1000 person-year).

Conclusions: Patients with MPN had higher incidence rates of WE, compared with those without MPN. Given the potentially dangerous outcomes associated with WE, physicians who care for patients with MPN should be aware of the risk of WE in this population.

402. Development of an Automated Risk Model for Drug-associated Inpatient Hypoglycemia

Almut G Winterstein,[1,2] Benjamin Staley,[3] Paul Kubilis,[1] Carl Henriksen,[1] Gloria Lipori,[4] Babette Brumback,[5] Thomas E Johns.[3] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Epidemiology, University of Florida, Gainesville, FL, USA; [3]Pharmacy Services, UF Health Shands Hospital, Gainesville, FL, USA; [4]Decision Support Services, UF Health Shands Hospital, Gainesville, FL, USA; [5]Biostatistics, University of Florida, Gainesville, FL, USA.*

Background: Hypoglycemia is recognized as one of the most prominent patient safety concerns in both inpatient and outpatient settings. The proliferation of electronic health record systems might allow automated alert systems that flag high-risk patients for prevention.

Objectives: This study aimed to construct a dynamic hypoglycemia (HG) risk model for hospitalized patients who receive antidiabetics (AD), for real-time use in inpatient electronic health records (EHR).

Methods: We established a retrospective cohort from the two largest University of Florida affiliated hospitals including all admissions aged ≥18 years between January 2012 and October 2013. We operationalized 45 risk factors for automated EHR retrieval and upon univariate and cluster analyses, retained 36 for model inclusion. For each of the first 5 hospital days with AD exposure, we predicted hypoglycemia (blood glucose <50 mg/dl) at the following hospital day using logistic regression with all risk factors and with subsets selected by experts or backward elimination. Predictive performance was validated with 100 bootstrap datasets.

Results: A total of 1264 HG events occurred in 60 929 risk days during the study period. Backward elimination models showed best performance with validated C-statistics between 0.83 (day 1) and 0.87 (days 3–5 combined). For days 3–5 predictions, 11.7% of patient days in the upper risk score decile had HG and accounted for 63.4% of all HG events. Highly predictive risk factors ($p < 0.01$) included low body weight, type 1 diabetes, coronary artery disease, CrCl, history of low BG, long-acting and high-dose insulin, NPO orders after long-acting insulin use, and sulfonylureas.

Conclusions: Risk models achieved excellent predictive validity. All risk factors were operationalized from discrete EHR fields and allow full automation for real-time prediction of high-risk patients.

403. Effect of Interpersonal Continuity of Care on Quality of Drug Use in Type 2 Diabetes

Anara Richi Dossa,[1,2,3] Jean-Pierre Grégoire,[1,2,3] Line Guénette,[1,2,3] Sophie Lauzier,[1,2,3] Jocelyne Moisan.[1,2,3] *[1]Faculty of Pharmacy, Laval University, Québec, QC, Canada; [2]Populations Health and Optimal Health Practices, CHU de Québec Research Center, Québec, QC, Canada; [3]Chair on Adherence to Treatments, Laval University, Québec, QC, Canada.*

Background: Interpersonal continuity of care (ICoC) is the cornerstone of primary care. However, it is unclear whether ICoC is associated with a better quality of drug use in type 2 diabetes patients.

Objectives: We assessed the association between ICoC and quality of drug use among individuals who initiated an oral antidiabetes drug (AD) treatment.

Methods: Using Quebec administrative databases, we carried out a cohort study of new users of oral AD, aged ≥18 years. Individuals were categorized according to tertiles of ICoC index (low, medium, and high) measured during the 1st year after oral AD initiation. Four quality indicators of drug use were assessed during the 2nd year of treatment: (1) persistence with AD, (2) compliance with AD among those considered persistent, (3) use of a guidelines-recommended angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ACEi/ARB), and (4) use of a guidelines-recommended lipid-lowering drug. The association between ICoC and the four quality indicators was assessed using multivariate logistic regression.

Results: The study included 60 924 individuals. Among them, 80.4% were persistent with their AD, 80.1% of persisters were compliant with their AD,

66.4% used an ACEi/ARB, and 66.3% used a lipid-lowering drug. Compared with individuals with a high ICoC, those with medium and low ICoC were less likely to be persistent (adjusted odds ratio = 0.85; 95%CI: 0.81–0.90 and 0.79; 0.75–0.83, respectively) and to be compliant with their AD (0.89; 0.84–0.94 and 0.77; 0.73–0.82, respectively). In contrast, the likelihood to use ACEi/ARB by individuals with high ICoC did not differ from those of individuals with medium and low ICoC (1.03; 0.98–1.08 and 1.01; 0.96–1.06, respectively). Compared with individuals with high ICoC, the likelihood to use a lipid-lowering drug was slightly lower for those with medium and low ICoC (0.94; 0.90–0.99 and 0.92; 0.88–0.97, respectively).

Conclusions: Those results emphasize the importance of ICoC in improving patients' medication adherence and lipid-lowering drugs use, but its role regarding ACEi/ARB use is not conclusive.

404. Do Individual Antihyperlipidemics Increase the Risk of Serious Hypoglycemia in Patients Receiving Sulfonylureas?

Charles E Leonard,[1,2] Warren B Bilker,[1,2,3] Colleen M Brensinger,[1] Xu Han,[1,2] James H Flory,[2,4] David A Flockhart,[2,5] Serena Cardillo,[2,6] Joshua J Gagne,[7] Sean Hennessy.[1,2,8] *[1]Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [2]Center for Pharmacoepidemiology Research and Training, Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [4]New York-Presbyterian Hospital, Columbia University College of Physicians and Surgeons / Weill Cornell Medical College, New York, NY, USA; [5]Department of Medicine, Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA; [6]Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [7]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [8]Department of Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA.*

Background: Concomitant use of sulfonylureas (SUs) and antihyperlipidemics is common. We hypothesized that some statins and fibrates might interact with SUs to increase the rate of hypoglycemia via inhibition of cytochrome P450 (CYP) 2C9 and/or 3A that inactivate SUs or through other mechanisms.

Objectives: The aim of this study was to assess whether initiation of an SU + antihyperlipidemic is associated with an increased rate of serious hypoglycemia within the first 180 days of concomitant therapy

Methods: Using 1999–2009 US Medicaid claims from five large states, we conducted three retrospective cohort studies—one each for glyburide, glipizide, and glimepiride. Exposure was defined as new concomitant use of the SU plus one of seven antihyperlipidemics, evidenced by prescription dispensings. Pravastatin was the reference exposure because it does not induce or inhibit CYPs. Outcomes were ascertained by emergency department or inpatient ICD-9 discharge diagnoses indicative of serious hypoglycemia (positive predictive value ~89%). Potential confounding was addressed by adjusting for multinomial high-dimensional propensity scores (PSs) included as continuous variables in a Cox proportional hazards model.

Results: Among 224 821, 239 151, and 128 900 concomitant users of antihyperlipidemics and glyburide, glipizide, and glimepiride, we identified 3184, 2889, and 1941 serious hypoglycemia events. Crude incidence rates per 100 person-years were 6.1 (95%CI 5.9–6.3), 5.1 (4.9–5.3), and 6.3 (6.0–6.6), respectively. PS-adjusted hazard ratios (HRs) for fenofibrate versus pravastatin were 1.34 (1.07–1.68), 1.24 (0.97–1.60), and 1.61 (1.28–2.04) for glyburide, glipizide, and glimepiride, respectively; HRs for gemfibrozil versus pravastatin were 1.50 (1.24–1.81), 1.36 (1.10–1.69), and 1.55 (1.20–2.00), respectively. No statins under study had elevated HRs.

Conclusions: We identified apparent health effects of interactions between SUs and fibrates, manifested as moderately increased risks of serious hypoglycemia. These effects may occur via CYP2C9 inhibition (a pharmacokinetic drug interaction) and/or peroxisome proliferator-activated receptor (PPAR) α pleotropism and/or PPARγ cross-reactivity (pharmacodynamic effects of fibrates).

405. Changes in Weight and Glycemic Control Following Intensification of Sulfonylurea Monotherapy with Insulin or Switch to Insulin Monotherapy

Jea Young Min,[1,2] Marie R Griffin,[1,2,3] Carlos G Grijalva,[1,3] Robert A Greevy,[1,4] Adriana M Hung,[1,2] Xulei Liu,[1,4] Christianne L Roumie.[1,2] *[1]Veterans Health Administration Tennessee Valley Healthcare System, Geriatric Research Education Clinical Center, HSR&D Center, Nashville, TN, USA; [2]Department of Medicine, Vanderbilt University, Nashville, TN, USA; [3]Department of Health Policy, Vanderbilt University, Nashville, TN, USA; [4]Department of Biostatistics, Vanderbilt University, Nashville, TN, USA.*

Background: Among patients receiving incident sulfonylurea monotherapy for type 2 diabetes mellitus (T2DM) and requiring further glycemic control, the benefits of adding insulin to sulfonylurea over switching to insulin monotherapy have not been established.

Objectives: The aim of this study was to describe changes in body mass index (BMI) and glycated hemoglobin (HbA1c) following addition of insulin or switch to insulin monotherapy among patients initially treated with sulfonylureas.

Methods: We assembled a retrospective cohort of US veterans with T2DM using dispensed prescriptions, demographics, and encounter data from the Veterans Health Administration and Medicare databases. Patients initiating sulfonylurea monotherapy from 2001 through 2008 and with a subsequent new insulin prescription fill were identified. Follow-up began 6 months after addition of insulin and continued until non-persistence on regimen, loss to follow-up, death, or end of study (30 September 2011). Sulfonylurea users adding insulin (SUL + INS) and those switching to insulin monotherapy (INS) were matched 1:1 using propensity scores based on baseline characteristics. BMI and HbA1c at baseline and at 12, 24, and 36 months of follow-up were compared between groups.

Results: Among 144 110 patients initiating treatment with a sulfonylurea, 5374 subsequently added insulin (3728 SUL + INS and 1646 INS). Propensity score matching yielded a cohort of 1596 patients in each treatment group. Median HbA1c at baseline was 8.3% in SUL + INS and 8.2% in INS patients. Median HbA1c decreased at 12 months to 7.3% and 7.1% in the SUL + INS and INS patients, respectively, and median HbA1c values remained constant at 24 and 36 months. Median BMI at baseline was 30.2 kg/m^2 in both groups and increased overtime (31.0 kg/m^2 at 36 months in both groups).

Conclusions: In new users of sulfonylureas who either added insulin or switched to insulin monotherapy, patients who switched to insulin monotherapy had a greater decrease in HbA1c, but the difference was modest. Body weight increased progressively in both groups.

406. Early Glycemic Control among Patients with Type 2 Diabetes and Initial Glucose-lowering Treatment: A 13-year Population-based Cohort Study

Reimar W Thomsen,[1] Lisbeth M Baggesen,[1] Elisabeth Svensson,[1] Lars Pedersen,[1] Helene Nørrelund,[1] Esben S Buhl,[2] Christiane L Haase,[2] Søren P Johnsen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Novo Nordisk Scandinavia AB, Copenhagen, Denmark.*

Background: Early intensive glucose-lowering therapy in type 2 diabetes reduces the risk of microvascular and possibly macrovascular complications. Little is known about temporal trends and achieved quality of glycemic control in large type 2 diabetes populations in community settings, who may differ from clinical trial participants.

Objectives: The aim of this study was to examine treatment initiation patterns and glycemic control in patients starting treatment for T2D.

Methods: Population-based cohort study of 38 418 adults with T2D and a first-time glucose-lowering drug prescription in Northern Denmark during 2000–2012 was carried out. Success in reaching HbA1c goals within 3–6 months was examined by the type of initial treatment and calendar year, using Poisson regression analysis.

Results: Ninety-one percent of all patients started with oral glucose-lowering drugs in monotherapy. Metformin initiation increased from 32% in 2000–2003 to 90% of all patients in 2010–2012. Pre-treatment HbA1c levels decreased substantially, from 8.9% (interquartile range (IQR), 7.6–10.7%) in 2000–2003 to 7.0% (IQR, 6.5–8.1%) in 2010–2012. More patients achieved an HbA1c target <7% (<53 mmol/mol) in 2010–2012 than in 2000–2003 (80% vs. 60%,

adjusted relative risk (aRR) = 1.10 [95%CI: 1.08–1.13]), and more achieved an HbA1c <6.5% (<48 mmol/mol) (53% vs. 37%, aRR = 1.07 [95%CI: 1.03–1.11]). Success rates in reaching HbA1c <6.5% were similar among patients <65 years without comorbidities. The average achieved HbA1c levels were similar for different initiation therapies, yet pre-treatment HbA1c and thus observed HbA1c reductions differed: 0.8 pp (from 7.3 to 6.5) on metformin, 1.5 pp (8.1 to 6.6) on sulfonylurea, 4.0 pp (10.4 to 6.4) on non-insulin combination therapies, and 3.8 pp (10.3 to 6.5) on insulin monotherapy.

Conclusions: Pre-treatment HbA1c level in new type 2 diabetes has decreased substantially during the last decade, and achieved glycemic control has improved. Still, many patients do not attain recommended HbA1c targets within the first 6 months of initial treatment.

407. Development, Implementation and Outcome Analysis of Semi-automated Alerts for Metformin Dose-adjustment in Renal Impairment

David F Niedrig,[1,2] Regina Krattinger,[1] Annika Joedicke,[1] Carmen Goett,[1] Gerd A Kullak-Ublick,[1] Guido Bucklar,[3] Stefan Russmann.[1,2] *[1]Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland; [2]Pharmaceutical Sciences, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland; [3]Medical Informatics, University Hospital Zurich, Zurich, Switzerland.*

Background: Lack of dose-adjustment of the oral antidiabetic drug metformin in impaired renal function is an important contributory cause of life-threatening lactic acidosis.

Objectives: We aimed to quantify and prevent this avoidable medication error in clinical practice.

Methods: We developed a sensitive algorithm for implementation into a hospital's clinical information system that automatically identifies patients if they have a current metformin prescription and their most recent estimated glomerular filtration rate (eGFR) value is <60 ml/minutes. If such patients are identified, real-time electronic alerts are sent to clinical pharmacologists and pharmacists, who evaluate respective cases by using all available information from electronic medical records. If appropriate, validated therapeutic recommendations based on current expert consensus and local guidelines are forwarded to the prescribing physicians.

Results: During 3 years since implementation of our alert program, the screening algorithm generated 2145 automated alerts (mean 1.5 per day). After expert evaluation, specific recommendations for changes of metformin therapy (dose reduction or stop) were issued for 355 cases. Follow-up was available for 256 cases, and among those, metformin dose was reduced or stopped in 209 cases, corresponding to a 79.3% compliance with our recommendations. During 3 years, we also identified eight patients with lactic acidosis associated with metformin and renal impairment. These had occurred in circumstances where no timely alerts could have been generated, such as metformin overdoses before hospital admission.

Conclusions: Automated sensitive screening for medication errors followed by highly specific expert evaluation and alerts can prevent medication errors in hospitals with high efficiency and efficacy. The clinical relevance of our alerts was underlined by several cases of lactic acidosis associated with metformin overdose where our alerts could not be generated but may have prevented adverse outcomes. This proof-of-concept program should be expanded to other clinically and economically relevant medication errors.

408. Benzodiazepines and Mortality: The Role of the Reference Group and the Source Population in Explaining Paradoxical Relations

Krista F Huybrechts, Robert Glynn, Moa Park, Raisa Levin, Elisabetta Patorno. *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.*

Background: Multiple studies have suggested benzodiazepines (BZD) are associated with an increased risk of mortality (up to 4.5-fold). An important challenge of research in this area is the selection of appropriate reference groups.

Objectives: The aim of this study was to explore the role of the reference group in relation to the source population when estimating the association between BZD and mortality.

Methods: The source cohorts for this population-based study were drawn from US commercial (Optum

Clinformatics, 04–13) and public (PACE-Pharmaceutical Assistance Contract for the Elderly, 95–05) health insurance databases. For every new BZD user, we selected a referent patient who had a medical visit (non-users) or initiated a comparator drug ±14 days of the BZD start. Informed by Glynn *et al.* (Epidemiol 2001), we selected drugs that had previously been associated with a decreased (statins) and an increased (loop diuretics) mortality risk. Proportional hazard models were run over a 6-month follow-up period in high-dimensional propensity score matched cohorts.

Results: The size of the cohort ranged from 1 256 630 to 30 367 matched pairs, depending on the data source and reference group. The base risk for BZD initiators was 9.8/1000 py in Optum and 117.1/1000 py in PACE, illustrating the vast differences in the characteristics of the source populations. The hazard ratio (HR) for the non-user comparison was 1.00 (95%CI, 0.96–1.04) for Optum and 0.76 (0.73–0.80) for PACE, suggesting no increased mortality risk associated with BZD use among Optum patients and a healthy-user bias among the frail and sicker PACE patients. The direction of the associations for the active comparators was consistent with expectations: HR = 2.40 (2.25–2.57) for statins, 0.75 (0.71–0.78) for loop diuretics in Optum, and 2.08 (1.88–2.30) and 0.86 (0.81–0.92) in PACE.

Conclusions: Different associations (protective to causal) were observed between BZD and mortality, depending on the source population and reference group used. Study reports should explicitly justify the selection of the source population and reference group and explore alternate choices in sensitivity analyses.

409. Opioids Use and Risk of Fractures in Rheumatoid Arthritis Patients: Results of a Canadian Epidemiological Study

Francisco A. Acurcio,[1,2] Cristiano S. Moura,[2,3] Sasha Bernatsky,[2,3] Louis Bessette,[4] Elham Rahme.[2,3] *[1]Department of Social Pharmacy, UFMG Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; [2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada; [3]Division of Clinical Epidemiology, McGill University, Montreal, QC, Canada; [4]Centre Hospitalier Universitaire de Québec, Laval University, Quebec City, QC, Canada.*

Background: Patients with rheumatoid arthritis (RA) are at an increased risk of osteoporosis and fractures.

Objectives: The aim of this study was to assess whether the use of opioids increases the risk of non-vertebral fractures in RA patients.

Methods: A nested case–control study was conducted with Quebec prescription drug, physician billing, and hospital discharge data. RA patients were identified using ICD-9/10 codes. Cases of fracture were identified with an algorithm previously validated. Controls were matched to cases (5:1) on age, sex, and date of cohort entry. The date of first fracture was defined as index date. Opioids exposure categories were defined as current use (for individuals with prescription supply that lasted up to or within 30 days the index date), recent past use (31–90 days), remote past use (91–365 days), or nonuse (never use or any use before 365 days). We further classified current use exposure according to the quartile distribution of the days of continuous supply in the year before the index date. Conditional logistic regression was used to calculate odds ratio (OR) and its 95% confidence interval (CI), adjusted for comorbidity score, indicators of RA severity, drugs influencing fracture risk, any hospitalization, and number of medical visits in the year before the cohort entry.

Results: 1723 cases were identified (8046 controls), mean age 76.2 ± 11.2 years. In total, 2543 patients (674 cases and 1869 controls) were exposed to opioids. Current use of opioids was associated with an increased risk of fracture when compared with nonuse: continuous use in the 1–20 days before the index date (OR = 11.49, 95%CI: 8.81–14.99), 21 to 155 days (OR = 1.75, 95%CI: 1.31–2.33), 156 to 355 days (OR = 1.54, 95%CI: 1.17–2.04), and 356 days or more (OR = 1.73, 95%CI: 1.30–2.30). No associations could be confirmed between the recent or remote past use of opioids and the risk of fractures. Other predictors of fracture were comorbidity score, history of osteoporosis, hospitalizations, medical visits, HRT, and current use of either antidepressants or acetylsalicylic acid.

Conclusions: We found an independent association between current use of opioids and fractures in this population.

410. Predictors for the Occurrence of Ischemic Cardiovascular Events among Users of High-potency Opioids (HPOs) and the Choice of HPO Treatment

Kathrin Jobski,[1] Bianca Kollhorst,[2] Edeltraut Garbe,[1] Tania Schink.[1] *[1]Clinical Epidemiology, Leibniz*

Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany; [2]Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany.

Background: In Germany, an extended-release (ER) combination of the high-potency opioid (HPO) oxycodone (OXY) and the opioid antagonist naloxone was approved in 2006. The combination provides similar analgesic efficacy to that of OXY while improving opioid-induced constipation (OIC). In 2012, concerns were raised regarding possible cardiovascular (CV) risks associated with opioid antagonists indicated for OIC treatment.

Objectives: The aim of this study was to explore predictors for (i) the occurrence of ischemic CV events among users of ER HPOs and (ii) the choice of treatment in new ER HPO users.

Methods: Using data from the German Pharmacoepidemiological Research Database (GePaRD), we identified a cohort of ER HPO users. Cohort entry was set to the first ER HPO dispensation between 2006 and 2011. The outcome was defined as hospitalization for either acute myocardial infarction (MI) or ischemic stroke (IS). Two separate logistic regression models were used to identify predictors for (i) the occurrence of MI/IS and (ii) the choice of ER HPO treatment among new users of OXY or oxycodone/naloxone (OXYN).

Results: During the study period, 309 936 ER HPO users were identified. Mean age at cohort entry was 70 years and 67% were female. Overall, 12 384 MS/IS events were observed. Among new ER HPO users, 40 395 patients started treatment with OXY and 39 152 received OXYN. Men were at higher risk for MI/IS than women (adjusted odds ratio (aOR): 1.25; 95% confidence interval: 1.15–1.35). Older age was also a strong predictor. Among pre-existing CV conditions, the highest aORs were found for cerebrovascular disease and transient ischemic attacks. Predictors of starting ER HPO treatment with OXYN were female sex, older age, and a diagnosis of cancer. Among CV risk factors, only peripheral vascular disease had a statistically significant impact with slightly decreased odds for OXYN (0.93; 0.89–0.98).

Conclusions: In our ER HPO cohort, older age, male sex, and known CV risk factors were predictors for MI/IS. Older age, female sex, and cancer were found to be predictors of starting treatment with OXYN instead of OXY, but no important channeling was observed for CV risk factors.

411. Opioid Analgesics and the Risk of Serious Infections among Patients with Rheumatoid Arthritis

Andrew D Wiese, Marie R Griffin, C Michael Stein, Edward F Mitchell, Jr., Carlos G Grijalva. *Department of Health Policy, Vanderbilt University, Nashville, TN, USA.*

Background: Patients with rheumatoid arthritis (RA) use opioid medications frequently and are at increased risk for infections. Although animal and *in-vivo* studies suggest that certain opioids impair crucial immune functions, the clinical implications of these effects remain unclear.

Objectives: The aim of this study was to determine if opioid use is associated with an increased risk of serious infections in patients with RA.

Methods: We conducted a self-controlled case series analysis on a retrospective cohort of patients with RA enrolled in Tennessee Medicaid (1995–2009). We excluded patients with life-threatening conditions at baseline and performed within-person comparisons of the risk of hospitalizations for serious infections during periods of opioid use and periods of non-use of opioids using conditional Poisson regression. Serious infections included hospitalizations for pneumonia, sepsis, meningitis/encephalitis, cellulitis, endocarditis, pyelonephritis, or infective arthritis/osteomyelitis. Fixed confounders were accounted for by design, and time-varying confounders including age, use of disease-modifying anti-rheumatic drugs, glucocorticoids, proton-pump inhibitors, seasonality, and nursing home residency were also accounted for in the analysis. New use of opioids was defined as use after 180 days without opioid exposure. To address potential confounding by indication (i.e., pain), we studied non-steroidal anti-inflammatory drug (NSAID) use as an active control.

Results: A total of 1763 hospitalizations for serious infection and 227 324 person-days of follow-up were analyzed. The adjusted incidence rate of serious infection was higher during periods of opioid use compared with no use (incidence rate ratio (IRR): 1.38 (95%CI: 1.14, 1.67)). The increased risk associated with new use of opioids was substantial (IRR): 2.56 (1.68,

3.89). Current use of NSAIDs was not associated with an increase in the incidence of serious infection (IRR: 1.12 (0.95, 1.32)).

Conclusions: For patients with RA, using within-person comparisons, the incidence of hospitalizations for serious infection was higher during opioid-exposed time periods compared with unexposed periods.

412. Increasing Benzodiazepine Use in the USA: Trends by Diagnosis, Age, Provider Type, and Co-prescribed Medication

Stephen Crystal,[1] Mark Olfson,[2] Shuai Wang,[2] Carlos Blanco.[2] *[1]Institute for Health, Health Care Policy and Aging Research, Rutgers, the State University of New Jersey, New Brunswick, NJ, USA; [2]New York State Psychiatric Institute, Columbia University, New York City, NY, USA.*

Background: Many studies have documented benzodiazepine-associated risks, particularly in the elderly. Co-prescription with opiates is particularly problematic.

Objectives: The objectives of this study were to provide national estimates of benzodiazepine prescribing in office-based medical care in the USA from 1995 to 2010; to examine use trends by diagnosis, demographics, provider type, and insurance coverage; and to examine co-prescription trends.

Methods: Analysis of nationally representative data on office-based physician visits from National Ambulatory Medical Care Survey (NAMCS) was carried out.

Results: Use increased steadily from 1995 to 2010, with the increase accelerating during the latter part of this period. The number of visits with a prescription of benzodiazepines per 100 population increased from 12.0 in 2003–2006 to 17.1 in 2007–2010 (22.5/100 for women vs. 11.6/100 for men) and from 29.4 to 41.7/100 at ages 65+ years. From 2003–2006 to 2007–2010, the proportion of visits that included a benzodiazepine prescription increased from 3.41% to 4.71% of privately insured visits, 5.13% to 7.99% of Medicare visits, 3.04% to 3.82% of Medicaid visits, 25.52% to 27.12% of psychiatrist visits, and 3.12% to 4.57% of non-psychiatrist visits. At ages 65+ years in 2007–2010, benzodiazepines were prescribed in 48.8% of visits with a diagnosis of anxiety disorders, 25.5% of depression visits, 27.2% of sleep disorder visits, and 11.3% of substance abuse disorder visits; they were co-prescribed in 19.2% of antidepressant visits, 19.5% of antipsychotic visits, 12.1% of stimulant visits, and 15.3% of opioid visits.

Conclusions: Use increased across all age groups between 2003–2006 and 2007–2010; almost 8% of Medicare visits in 2007–2010 included such prescriptions. Benzodiazepines were co-prescribed at high and increasing rates with antidepressant, antipsychotic, stimulant, and opioid medications. Exclusion of benzodiazepines from the Medicare prescription drug enacted in 2006 seems not to have slowed the growth, highlighting the difficulty of influencing use. Nevertheless, given concerns over safety in older populations and with opioid co-prescription, increased clinical and policy attention is needed to minimize and manage these risks.

413. Long-term Users of z-hypnotics—High Level of Co-medication with Other Addictive Drugs

Solveig Sakshaug, Vidar Hjellvik, Christian Berg, Marte Handal, Svetlana Skurtveit. *Pharmacoepidemiology, Norwegian Institute for Public Health, Oslo, Norway.*

Background: Z-hypnotics (zopiclone/eszopiclone and zolpidem) are increasingly used for treatment of insomnia. These are approved for short-term treatment of 2–4 weeks, but the duration of treatment is often much longer in clinical practice.

Objectives: The aim of this study was to study long-term use of z-hypnotics in new users and co-medication with benzodiazepines (BZD) and opioids.

Methods: Data on z-hypnotics, BZD, and opioids dispensed to all adult outpatients in Norway (aged 18 years and over) in the period 2007–2013 were obtained from the Norwegian Prescription Database.

Patients with no recorded z-hypnotics during 730 days prior to the date of the first recorded prescription in 2009 were defined as new users. The users were followed over 4 years from the date of the first prescription in four 365 days periods (1st–4th year). The treatment intensity in each period was measured in number of defined daily doses (DDDs). Co-medication with BZD and/or opioids was studied in long-term users (patients with repeated prescriptions of z-hypnotics in all of the 4 years).

Results: The number of new users of z-hypnotics in 2009 was 92 911. The incidence was 2.2% in men and 3.4% in women. Eighty-five percent started with

zopiclone and 15% with zolpidem. Fifty-five percent of the new users had no refills during the 1st year; 13 996 (17%) of the new users became long-term users (15% for men and 18% for women). The proportion of long-term users was similar in patients initiated with zopiclone and zolpidem and increased with age in both genders. The yearly amount prescribed to long-term users increased from a median of 120 DDDs in the 2nd year to 160 DDDs in the 4th year of follow-up.

In each year of follow-up, around one-third of the long-term users of z-hypnotics also used BZD and/or opioids.

Conclusions: Among new users of z-hypnotics, nearly 20% became long-term users, and the amount dispensed indicated regularly use. BZD and opioids were also commonly prescribed to the long-term users. The results indicate not recommended use of z-hypnotics with regard to both duration of treatment and co-medication with other addictive drugs.

414. Prenatal Antidepressant Exposure and the Risk of Autism Spectrum Disorder and Attention-deficit Hyperactivity Disorder

Kenneth KC Man,[1] Esther W Chan,[1] David R Coghill,[2] Patrick Ip,[3] Emily Simonoff,[4] Wallis CY Lau,[1] Ian CK Wong.[1] *[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong; [2]Division of Medical Science, School of Medicine, University of Dundee, Dundee, UK; [3]Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong; [4]Institute of Psychiatry and NIHR Biomedical Research Centre for Mental Health, Kings College London, London, UK.*

Background: Recent studies suggested that prenatal exposure of selective serotonin reuptake inhibitors (SSRIs) may be associated with increased risk of autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). However, confounding has not been comprehensively excluded.

Objectives: The aim of this study was to investigate the association between SSRIs and ASD and ADHD in a large healthcare system.

Methods: 429 645 children who were delivered in public hospital were identified using the Hong Kong population-based electronic medical records on the Clinical Data Analysis & Reporting System (2001–2014). Using a case–control study design, we evaluated the association between ASD or ADHD and prenatal exposure of SSRIs. Further analyses using disease risk score (DRS) matching (1:10) and within-patient study design, case–time–control (CTC), were conducted to address residual confounding. The risks of ASD and ADHD were estimated using odds ratios (ORs) from logistic regression.

Results: Among 429 645 children identified, 299 672 were included in the analysis; 4208 and 2706 children were diagnosed with ASD and ADHD, respectively. 0.88% of ASD and 1.22% of ADHD children were having prenatal SSRIs exposure compared with 0.6% in controls. The adjusted ORs of ASD and ADHD are 1.35 (95%CI 0.94–1.93) and 2.12 (95%CI 1.44–3.11), respectively. The findings were similar in DRS matched model. In contrasts, no association was found in CTC analysis (OR = 1.12, 95%CI 0.83–1.53 for ASD; OR = 0.81, 95%CI 0.58–1.12 for ADHD). Alternative analyses using non-SSRI antidepressant as exposure showed similar results. The CTC ORs for ASD and ADHD were 1.08 (95%CI 0.81–1.44) and 1.02 (95%CI 0.75–1.39), respectively. In validation analysis using insulin as negative control, no association was found in CTC analyses (OR = 1.13, 95%CI 0.31–4.04 for ASD; OR = 1.15, 95%CI 0.25–5.28 for ADHD).

Conclusions: This study does not support the hypothesis that prenatal SSRIs exposure increased the risk of ASD or ADHD in children. These results suggest that the risk of ASD and ADHD observed with prenatal SSRI exposure is likely confounded by maternal underlying medical conditions and genetic factors.

415. Use of ADHD Drugs in Children and Adolescents in the Nordic Countries 2008–2012—A Population-based Study

Kari Furu,[1] Øystein Karlstad,[1] Helga Zoega,[2] Jaana Martikainen,[3] Helle Kieler,[4] Shahram Bahmanyar,[4] Anton Pottegård.[5] *[1]Dept of Pharmacoepidemiology, Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway; [2]Centre of Public Health Science, University of Iceland, Reykjavik, Iceland; [3]Research Department, The Social Insurance Institution, Helsinki, Finland; [4]Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [5]Clinical Pharmacology, Dept of Public Health, University of Southern Denmark, Odense, Denmark.*

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Background: Hyperkinetic disorder or attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric conditions of childhood and is estimated to affect 3–6% of children. Use of stimulants to treat ADHD has increased several-fold over the past two decades throughout the world. We use the Nordic prescription databases to examine the individual use of ADHD drugs in children and adolescents.

Objectives: The aim of this study was to assess the annual prevalence and incidence of use of ADHD drugs during 2008–2012 in the entire Nordic child population aged 6–17 years comprising about 3.5 million inhabitants.

Methods: Data on ADHD drugs dispensed from pharmacies were retrieved from the nationwide prescription registers in each of the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) with complete coverage of prescribed drug use in the outpatient setting for all inhabitants. ADHD drugs were methylphenidate (N06BA04), atomoxetine (N06BA09), amphetamine (N06BA01) and dexamphetamine (N06BA02). Data were pooled in one database and analysed as annual cross sections for 2008–2012. Period prevalence was defined as the number of users of ADHD drugs per year, while incidence was defined as the number of new users per year (730 days run-in). The denominator was the gender-specific and age-specific population in each country of the same year.

Results: In 2008, 47 226 individuals (1.3% of all Nordic children aged 6–17 years) were dispensed a stimulant at least once, increasing further to 76 363 (2.1%) in 2012. The annual prevalence increased from 1.9% to 3.1% for boys and from 0.6% to 1.1% in girls during the study period. Methylphenidate was the predominant stimulant used in all years. The proportion of extended release formulation of methylphenidate increased during the study period. The incidence was 0.55% for boys and 0.21% for girls in 2008, increasing to 0.69% and 0.33% in 2012, respectively.

Conclusions: In the Nordic countries, both the prevalence and the incidence of use of ADHD drugs increased in both gender during the 5-year period 2008–2012. The male/female prevalence ratio declined slightly from 2008 to 2012.

416. Behavioral Effects of Fetal Antidepressant Exposure in a Norwegian Cohort of Discordant Siblings

Ragnhild Eek Brandlistuen,[1,2] Eivind Ystrøm,[1,2] Malin Eberhard-Gran,[2] Irena Nulman,[3] Gideon Koren,[3] Hedvig Nordeng.[1,2] *[1]University of Oslo, Oslo, Norway; [2]Norwegian Institute of Public Health, Oslo, Norway; [3]Hospital for Sick Children, Toronto, Canada.*

Background: Potential adverse effects of prenatal antidepressant exposure on child neurodevelopment are still debated. The possibility that associations are due to genetic or familial environmental risk factors rather than antidepressant use *per se* cannot easily be ruled out in conventional pharmacoepidemiological studies.

Objectives: Our objective was therefore to evaluate the association between prenatal antidepressant exposure and behavioral problems in children to the age of 3 years using a sibling-controlled study.

Methods: This study used data on 20 180 siblings from the population-based Norwegian Mother and Child Cohort Study recruited between 1999 and 2008. Women reported antidepressant use in three self-completed questionnaire at gestational weeks 17 and 30 and 6 months postpartum. Child Behavioral Checklist scales were used to assess externalizing and internalizing behavioral problems by questionnaires sent to mothers 18 and 36 months postpartum. We performed unmatched and matched sibling analyses using both random-effects and fixed-effects linear models, respectively, to determine potential effects of antidepressant exposure.

Results: Prenatal exposure to antidepressants was associated with increased levels of anxiety symptoms in 3-year-old children after adjusting for maternal familial effects and maternal symptoms of depression. Effect of prenatal exposure to antidepressants was specific to anxiety, and not associated with emotional reactivity, somatic complaints, sleep problems, attention problems, or aggression.

Conclusions: Using a sibling design, we showed that prenatal antidepressant use was specifically associated with increased anxiety symptoms in 3-year-old children after adjusting for maternal familial factors and maternal symptoms of anxiety and depression.

417. Cardiac Risk Associated with Methylphenidate in Pediatric Patients with Attention Deficit Hyperactivity Disorder (ADHD): Self-controlled Case Series Study in Korea

Ju-Young Shin,[1] Shin Haeng Lee,[1] Han Na Shin,[1] So-Hyun Choi,[1] Nicole L Pratt,[2] Elizabeth E

Roughead,[2] Byung-Joo Park.[3] *[1]DUR Information, Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [2]School of Pharmacy and Medical Sciences, Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia, SA, Australia; [3] Department of Preventive Medicine, Seoul National University, College of Medicine, Seoul, Republic of Korea.*

Background: Since the cases of serious cardiac adverse event associated with methylphenidate was reported, many epidemiology studies have been performed. However, previous studies reported conflicting findings with limited statistical power and low absolute risk of an event.

Objectives: The aim of this study was to evaluate the association between methylphenidate use and adverse cardiac outcomes using the self-controlled case series study design.

Methods: We used the Korea Health Insurance Review and Assessment (HIRA) claims database between 1 January 2009 and 31 December 2012. Pediatrics patients 18 years of age and younger with attention deficit hyperactivity disorder (ADHD) (ICD-10 code F90) who had records of a cardiac outcome (sudden cardiac death (ICD-10 code I46.1, I46.9), myocardial infarction (I29), stroke (I63), hypertensive disease (I10-I15), or arrhythmias (I44-I49 except I46.1, I46.9)) and at least one prescription for methylphenidate before the end of 2012 were identified. Incident rate ratios (IRR) for cardiac outcomes in periods of methylphenidate exposure compared with unexposed periods were calculated. We estimated the IRR and their 95% confidence intervals (CI) using conditional Poisson regression.

Results: The total number of 2945 eligible participants were identified and included in the final analysis. The median period of exposure was 2.5 years with follow-up (Q1–Q3, 1.3–3.8). The study population consisted of 77% boys, whose median age was 15 years (Q1–Q3, 12–17). An increased risk was observed in the 1–30 days post initiation (IRR = 2.08, 95%CI: 1.98–2.18), 31–60 days (IRR = 1.84, 95%CI: 1.70–1.99), and post 60 days (IRR = 1.39, 95%CI: 1.27–1.51).

Conclusions: Our self-controlled case series study suggests an increased risk of cardiac events associated with methylphenidate use.

418. Drug Utilization Study of Childhood Epilepsy

Chintan Dave,[1] Abraham Hartzema,[1] Edgard Andrade,[2] Almut Winterstein.[1] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Department of Pediatrics- Division of Pediatric Neurology, University of Florida, Gainesville, FL, USA.*

Background: To date, no large scale study has examined the drug utilization patterns of children with epilepsy.

Objectives: The aim of this study was to conduct a drug utilization study in children aged 0–18 years in a large healthcare claims database.

Methods: We utilized Medicaid Analytic eXtract (MAX) data from 29 states for the years 2004–10 for this study. We identified epileptic patients as those who had two ICD9 codes for epilepsy (345.xx or 780.39) at least 30 days apart but within 180 days. We identified epilepsy subtypes using an algorithm that weighted claims from inpatient and emergency department visits more than outpatient claims. We categorized age (0–2, 2–6, 6–10, and 10–18 years) and epilepsy (generalized, partial, and other) and estimated the prevalence of antiepileptic agents for all subtypes. For each antiepileptic agent, we looked at all FDA-approved indications to identify the age cutoffs for each agent. We quantified the off-label use based on FDA-approved age cutoff.

Results: For the years 2004–2010, we identified 298 447 patients with epilepsy. For all epilepsy subtypes, levetiracetam had the highest prevalence of use with more than 35% in generalized epilepsy and 30% in partial epilepsy. Diazepam had the second highest prevalence of use (>30%). The use of topiramate increased from 12% in ages 0–6 years to more than 35% in the later years, regardless of epilepsy subtype. The overall use of benzodiazepines, while substantial, declined as age increased. Different age and epilepsy subtypes had different patterns of antiepileptic drug use. As expected, the prevalence of off-label use was high during the first few years of life at 47.2%. For instance, valproic acid prevalence of use, while not approved for this age, reached as high as 7% during the first year of life.

Conclusions: To date, this is one of the largest DUR studies conducted on children with epilepsy. The high

prevalence of off-label medications emphasizes the need for more safety and effectiveness studies for this population.

419. Labor Induction and Offspring Risk of Autism Spectrum Disorder

Anna S Oberg,[1,2] Brian M D'Onofrio,[3] Martin E Rickert,[3] Sonia Hernandez-Diaz,[1] Brian T Bateman.[4,5]
[1]Department of Epidemiology, Harvard T. Chan School of Public Health, Boston, MA, USA; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [3]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA; [4]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [5]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA.

Background: Recently, a large population-based study identified an association between induction of labor and the risk of autism spectrum disorder (ASD) in the offspring. However, the study has been criticized for being unable to control for all relevant confounding factors.

Objectives: The aim of this study was to examine the association between labor induction and ASD in Swedish register data, with ability to include a sibling comparison. This approach controls for all confounders shared by full siblings, including shared genes, early environment, and stable maternal factors, thus providing a more valid causal estimate of the effect of induction.

Methods: Linkage between registers in Sweden facilitated a nation-wide cohort study of all live births in Sweden from 1991 to 2001. Exposure was defined by the presence or absence of induction of labor prior to delivery. The outcome was identified by specialist diagnosis of ASD in offspring through the end of 2009. In the initial analysis, we assessed the association between labor induction and offspring ASD using Cox proportional hazard regression. We then adjusted for stable maternal characteristics and factors unique to each pregnancy. Finally, we accounted for all factors shared by full siblings using a fixed-effects model in which the underlying hazard is allowed to vary between mothers.

Results: The full cohort included 978 981 births, of which 10 329 were diagnosed with ASD (1.1%). Labor induction was significantly associated with offspring ASD in the baseline model (HR, 1.27; 95%CI, 1.19 to 1.35). After adjustment for all measured factors, the association to both ASD was still present (HR, 1.17; 95%CI, 1.09 to 1.27). However, when further adjustment was made using a fixed-effects model (comparing outcomes in siblings discordant with respect to induction) to account for all factors shared by full siblings, labor induction was no longer associated with offspring ASD (HR, 1.04; 95%CI, 0.85 to 1.27).

Conclusions: In this nation-wide sample of live births, we observed no meaningful relationship between induction of labor and the risk for ASD. Our findings suggest that concern about this outcome should not factor into the clinical decision about whether to induce labor or not.

420. Time Series Analysis of the Impact of Adverse Media on Statin Dispensing and Discontinuation in Australia

Andrea L Schaffer,[1] Nicholas A Buckley,[2] Timothy Dobbins,[3] Emily Banks,[3] Sallie-Anne Pearson.[1,4]
[1]Faculty of Pharmacy, University of Sydney, Sydney, New South Wales, Australia; [2]School of Pharmacology, University of Sydney, Sydney, New South Wales, Australia; [3]National Centre for Epidemiology and Population Health, The Australian National University, Canberra, Australian Capital Territory, Australia; [4]School of Public Health, University of Sydney, Sydney, New South Wales, Australia.

Background: The mass media is an important source of medical information for the general public and has the potential to influence both patient and prescriber behaviour. In October 2013, an Australian science journalism programme aired a two-part series critical of HMG-CoA reductase inhibitors ('statins'). After the programme, anecdotal evidence suggested that many statin users stopped taking them.

Objectives: The aim of this study was to examine the programme's impact on statin dispensing and discontinuation in Australia.

Methods: We obtained dispensing data for a 10% sample of Australians (July 2009 to June 2014). We performed an interrupted time series analysis of weekly statin dispensing and weekly statin discontinuation rates,

overall and stratified by cardiovascular risk category (estimated using dispensed medicines). We used an autoregressive integrated moving average (ARIMA) model to adjust for autocorrelation, as well as seasonal and long-term trends. Proton pump inhibitor (PPI) dispensing was used as a comparator.

Results: In our sample, 191 833 people were dispensed an average of 26 946 statins weekly over the study period. After the programme, there was a 2.6% (95% CI, 1.4–3.8%, $p < 0.001$) reduction in statin dispensing, equivalent to 14 005 fewer dispensings Australia-wide every week. Dispensing decreased by 6.0% (3.7–8.3%, $p < 0.001$) in individuals at low risk of cardiovascular events and 1.9% (0.4–3.5%, $p = 0.01$) in individuals at high risk. On the week of the programme, there was a 28.8% (15.4–43.7%, $p < 0.001$) increase in statin discontinuation, decaying by 9% per week; over 8 months, an estimated 24 291 additional Australians ceased statin treatment. Discontinuation occurred in all risk categories. There were no significant perturbations in PPI use following the programme.

Conclusions: The programme was watched by nearly 1.5 million Australians; statin dispensing changed significantly in the 8 months following the programme with no signs of abatement by June 2014. There were 448 160 fewer statins dispensed, estimated to be equivalent to 56 020 people affected, including high-risk individuals.

421. Pragmatic Randomized Trials in Practice: How Can We Overcome the Hurdles? (Sponsored by the CER Special Interest Group)

Sebastian Schneeweiss,[1] Joshua Gagne,[1] Jeffrey Brown,[2] Jeremy Rassen,[3] Hans-Georg Eichler,[4] Geral Dal Pan,[5] Dorothee Bartels.[6] *[1]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Department of Population Medicine, Harvard Medical School, Boston, MA, USA; [3]Chief Science Officer, Aetion, Inc., New York, NY, USA; [4]European Medicines Agency, London, UK; [5]Office of Surveillance and Epidemiology, US Food and Drug Administration, Washington, DC, USA; [6]Pharmacoepidemiology, Boehringer Ingelheim, Ingelheim, Germany.*

Background: Decision-makers need evidence that support causal conclusions on the safety and effectiveness of medications shortly after their marketing and thereafter in regular time intervals. There have been substantial developments in conducting pharmacoepidemiology studies of high validity analyzing and repeatedly reanalyzing regularly refreshing streams of data recorded during the provision and administration of health care. Such rapid-cycle analytics does not need to compromise the quality of the study conduct and its reporting. There is some variation in how this is approached from an epidemiological and a technical perspective, and there are new questions arising on how decision-makers in regulation or industry are dealing with an ongoing stream of new treatment effect estimates.

Objectives: The objectives of this study were to illustrate current methodologies and share selected experiences with rapid-cycle database analytics including the consequences for communication and decision-making and to lay out future directions for accelerating the analysis of very large healthcare databases (claims and EHR) without compromising a high degree of validity so that causal interpretation can be supported for improved decision-making.

Description: Topic areas and speakers (confirmed):

- Rapid-cycle analytics in practice (1): Structure and performance of the FDA Sentinel PROMPT analytic modules (Josh Gagne and Jeff Brown)
- Rapid-cycle analytics in practice (2): Performance and validity of the Aetion evidence platform for healthcare databases (Jeremy Rassen)
- How does rapid-cycle analytics help enable adaptive licensing of medical products? (Hans-Georg Eichler, EMA),
- What does rapid-cycle analytics mean for ongoing safety communication? (Gerald Dal Pan, FDA)
- How do pharma companies position findings from rapid-cycle analytics? (Dorothee Bartels, BI)

Structure: The two technical presentations will spend 15 minutes each to present their approach and technology. This is followed by three 10-minute presentations by stakeholders sharing their thoughts on implications of RCA. Sebastian Schneeweiss will moderate 30 minutes of audience contributions using a set of prepared back-up questions.

422. Pragmatic Randomized Trials in Practice: How Can We Overcome the Hurdles? A CER SIG-sponsored Symposium

Mary Prince Panaccio,[1] Tom MacDonald,[2] Liam Smeeth,[3] Kourtney Davis,[4] Sarah Daugherty,[5] Cynthia

J Girman.[6,7] [1]*Evidence-Based Medicine, Sanofi-US, Bridgewater, NJ, USA;* [2]*Medicines Monitoring Unit, Ninewells Hospital & Medical School, Dundee, UK;* [3]*Clinical Epidemiology, London School of Hygiene and Tropical Medicine, University of Manchester, London, UK;* [4]*Worldwide Epidemiology, GlaxoSmith Kline, Collegeville, PA, USA;* [5]*CER Methods and Infrastructure, Patient-Centered Outcome Research Institute, Washington, DC, USA;* [6]*CERobs Consulting, LLC, Chapel Hill, NC, USA;* [7]*Epidemiology, Gillings Global School of Public Health, University of North Carolina, Chapel Hill, NC, USA.*

Background: Evidence on which therapeutic intervention provides the most value to patients, physicians, and payers is essential in the current environment of limited healthcare resources and needs to be addressed in a timely manner for decision-making. Randomized controlled blinded trials (RCTs) are the basis for regulatory approval but may not reflect routine clinical practice. Although decision makers prefer more real-world comparative effectiveness and safety evidence, the non-randomized nature of such studies can limit their interpretability. Pragmatic randomized clinical trials (pRCTs) can fill this void by ensuring baseline comparability of groups through randomization and provide information in routine clinical care settings based on broader, more diverse patient populations. Unfortunately, pRCTs have a number of hurdles that limit implementation.

Objectives: The aim of this study was to provide an overview of (a) definition and hurdles of pragmatic trials to address critical comparative research questions in the post-marketing and pre-launch space and (b) several case studies and initiatives to illustrate the changing pRCT landscape, including developments and solutions for ongoing challenges in implementation.

Description: An overview will be given of the definition and hurdles of pRCTs and their role in evidence generation for various stakeholders. Several case studies will be presented, including pilot pRCTs in UK primary care computerized health records and pragmatic studies in hypertension. An EMR-enabled pRCT initiated prior to medicine authorization in Salford, UK, will also be presented. We will review the Innovative Medicines Initiative project GetReal aimed at determining how to generate evidence on relative effectiveness earlier in drug development, as well as PCORnet, the national Patient-Centered Clinical Research Network of healthcare facilities using electronic medical records for research that matters to patients. Each speaker will discuss pRCT challenges, including external validity and how they may be overcoming them. A moderated Q&A will wrap the session.

423. Building a Sustainable Surveillance System to Monitor the Use and Safety of Medical Products in Pregnancy

Susan Andrade,[1] Susana Perez-Gutthann,[2] Wei Hua,[3] Alison Kawai,[4] David Martin,[5] Marsha Reichman,[3] Darren Toh.[4] [1]*Meyers Primary Care Institute, Worcester, MA, USA;* [2]*RTI Health Solutions, Barcelona, Spain;* [3]*U.S. Food and Drug Administration, Silver Spring, MD, USA;* [4]*Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA;* [5]*Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA.*

Background: Evidence about the safety of medical products in pregnant women relies heavily on observational data. However, it has been extremely challenging to create a sustainable and scalable infrastructure to support large-scale population-based surveillance of medical product safety in pregnancy. Numerous regional, national, and international efforts have attempted to create such a system, with varying degree of success.

Objectives: This workshop will describe recent efforts by the US FDA in creating a new capability for a population-based surveillance of medical product use and safety in pregnancy within the Mini-Sentinel pilot project.

Description: The workshop will cover (1) FDA's regulatory need for monitoring the safety of medical products in pregnant women and how Mini-Sentinel can help support its regulatory mission and (2) a series of completed and ongoing activities in Mini-Sentinel designed to build a surveillance system for assessing medical product exposure and safety in pregnancy. We will describe the design of the system, accomplishments to date, challenges, and future directions.

(1) Introduction and aims of the workshop (Toh, 5 minutes)
(2) The use of Mini-Sentinel to help monitor the use and safety of medical products in pregnancy (10 minutes)

a. CBER goals and perspective (Martin)
b. CDER goals and perspective (Reichman)
(3) Rationale, design, and findings of complete and ongoing activities (45 minutes):
a. Framework for evaluating pregnancy outcomes following vaccination (Hua)
b. Framework for evaluating infant outcomes following maternal prenatal vaccination (Kawai)
c. Design of a reusable analytic tool to monitor drug exposure in pregnant women (Andrade)
d. Prevalence of selected medications in pregnant women (Reichman)
(4) Comments from external stakeholder (Perez-Gutthann, 10 minutes)
(5) Discussion with stakeholder and audience (20 minutes)

424. Historical Comparator Studies: Strengths, Limitations, and Analytical Considerations in Using Historical Pooled Clinical Data for Evaluating Efficacy and Safety of New Therapies

Michael Kelsh,[1] Chia-Wen Ko,[2] Victoria Chia,[1] Donna Przepiorka,[2] Samy Suissa.[3] *[1]Center for Observational Research, Amgen Inc, Thousand Oaks, CA, USA; [2]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA; [3]McGill University, Montreal, QC, Canada.*

Background: For rare diseases, particularly when no effective treatments are available and where disease prognosis is poor or dismal, accelerated or conditional approvals may provide earlier access to treatments for these patients with a high unmet need. For these situations, regulatory agency decisions on drug approval often need to rely on Phase II single-arm studies. Historical comparator data likely provide the most robust proxy information for evaluating the efficacy and safety experience among target patient populations.

Objectives: The objectives of this study were to discuss potential strengths, limitations, and value of historical comparator studies in the context of evaluating new therapies; to use a recently completed historical comparator study as a case study to highlight study design, implementation, and analysis issues; and to provide a forum for discussion among regulatory, academic, and pharmaceutical industry scientists on these studies. This symposium would benefit all parties involved in drug development by providing a better understanding on the design and analysis of historical comparator studies.

Description: Historical comparator studies may represent a more robust and feasible alternative to expert clinical opinions, literature reviews, and meta-analyses when Phase III clinical trial data are not available, and there is a need for comparative information on safety and efficacy of current standard of care for serious diseases with unmet needs. Essentially pooled analyses, these studies can be affected by challenges such as study heterogeneity, lack of consistent outcome and exposure definitions, comparability to current clinical practices, and potential study biases (e.g., selection, immortal time, and misclassification bias). The recently completed historical comparator study for a rare oncology outcome (relapsed/refractory acute lymphoblastic leukemia [R/R ALL]) and regulatory review of that data provide an opportunity to review and discuss study design, analysis, and study bias issues.

425. PROTECT: The Challenges and Successes

Robert Reynolds,[3] Xavier Kurz,[2] Stella CF Blackburn.[1] *[1]Real World Late Phase Research, Quintiles, Reading, Berkshire, UK; [2]Monitoring and Incident Management, European Medicines Agency, London, UK; [3]Epidemiology, Pfizer, New York, NY, USA.*

Background: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) was one of the first consortia to be selected for funding by the Innovative Medicines Initiative—a 2 billion European Public Private Partnership. PROTECT was led by the European Medicines Agency and brought together 35 partners from regulatory authorities, academia and the pharmaceutical industry.

Objectives: The aim of this study was to examine what contributions PROTECT has made to the pharmacovigilance field and the challenges faced.

Description: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) was one of the first consortia to be selected for funding by the Innovative Medicines Initiative—a 2 billion European Public Private Partnership. PROTECT was led by the European Medicines Agency and brought together 35 partners from regulatory authorities, academia and the pharmaceutical

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industry. PROTECT's aim was and is to strengthen the monitoring of the benefit–risk of medicines in Europe by researching into methods to:

- enhance data collection directly from consumers of medicines in their natural language in several European Union countries, using modern tools of communication;
- improve early and proactive signal detection from spontaneous reports, electronic health records and clinical trials;
- develop, test and disseminate methodological standards for the design, conduct and analysis of pharmacoepidemiological studies applicable to different safety issues and using different data sources;
- develop methods for continuous benefit–risk monitoring of medicines, by integrating data on benefits and risks from clinical trials, observational studies and spontaneous reports, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods;
- test and validate various methods developed in protect using a large variety of different sources in the European Union (e.g. clinical registries) in order to identify and help resolve operational difficulties linked to multi-site investigations.

The IMI funding for PROTECT finished in 2015. This symposium reviews the challenges and successes of PROTECT and how it has advanced pharmacovigilance in Europe.

Speakers and Presentations

Dr Robert Reynolds: What difference does PROTECT make to industry standards and practice?

Dr Xavier Kurz: What difference will PROTECT make to standards and regulatory practice?

Dr Stella Blackburn: Successes and challenges of collecting data from consumers as part of a public private consortium.

426. Challenges of Introducing New Vaccines in Resource-Limited Settings (Co-Sponsored by the Vaccine Special Interest Group & the Brighton Collaboration Foundation)

Huifeng Yun,[1] Daniel Weibel,[2] Adam Yadong Cui,[3] Laurence Baril,[4] Alena Khromova,[5] Fabien Diomande.[6] *[1]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Erasmus Medical Center, Rotterdam, The Netherlands; [3]Merck Sharp & Dohme Corp, North Wales, PA, USA; [4]GlaxoSmithKline, Wavre, Belgium; [5]Sanofi Pasteur Ltd, Toronto, Canada; [6]WHO, Geneva, Switzerland.*

Background: Taking advantage of the biotechnology revolution and new funding organizations (e.g., Gates Foundation), several new vaccines have been developed against major killers (e.g., Ebola, dengue, malaria, and meningitis A). Because the main target population for these new vaccines is in low-income or middle-income countries (LMIC), considerable challenges face key stakeholders (manufacturers and local and international authorities) in conducting adequate vaccine post-approval safety and effectiveness studies.

Objectives: The objectives of this study were (1) to understand the difference between traditional and current environment for introduction of new vaccines in LMIC in terms of post-approval safety and effectiveness evaluation; and (2) to describe specific adaptations needed using new vaccine examples.

Description: The symposium will be devoted to sharing experiences and plans for safety and effectiveness monitoring activities for several new vaccines using concrete examples. Manufacturers will discuss the various adaptations they are making to meet the desired objectives in the LMIC environment (e.g., timeliness, quality, validity, and regulatory). International institutions will share their perspectives on requirements for these vaccines. Lessons learned will inform introduction of new vaccines or drugs in LMICs.

Symposium format:

(1) Introduction of VAXSIG and Symposium
(2) Experience with Meningitis A vaccine (WHO)
(3) Examples of new vaccines

    Ebola vaccine (Merck)Malaria vaccine (GSK) Dengue vaccine (Sanofi-Pasteur)

(4) Panel discussion

Moderators: Daniel Weibel, University of Rotterdam; Huifeng Yun, University of Alabama at Birmingham.

Panelists: Laurence Baril (GSK Vaccines), Adam Cui (Merck), Fabien Diomande (WHO/US CDC), Alena Khromava (Sanofi-Pasteur). Co-sponsored by The Vaccine Sig and the Brighton Collaboration Foundation.

427. Evaluating Risk Evaluation and Mitigation Strategies (REMS): Lessons Learned and Future Opportunities with a Focus on Opioid Analgesics

Caitlin A Knox,[1] Gerald J Dal Pan,[2] Paul M Coplan,[3] Stephan F Lanes.[1] *[1]Safety and Epidemiology, HealthCore, Andover, MA, USA; [2]US Food and Drug Administration, Silver Spring, MD, USA; [3]Purdue Pharma L.P., Stamford, CT, USA.*

Background: Risk Evaluation and Mitigation Strategy (REMS) has been developed to reduce the incidence adverse events and ensure benefits outweigh risks. Part of any REMS entails evaluation to ensure the REMS is effective. REMS evaluation studies face unique challenges because of the goals and heterogeneous nature of REMS programs that can require creative approaches.

Objectives: This workshop will give an overview of the methods used and challenges encountered in REMS evaluation studies with a focus on opioid analgesics. We will engage the audience with REMS evaluation examples and experiences from regulatory, industry, and data partners. Furthermore, this workshop seeks to engage the ICPE audience in a discussion about REMS evaluation studies with a focus on opioid analgesics.

Description: This workshop will start with the moderator, Caitlin Knox, providing an overview of the goals of the session and introducing the topic of REMS, as well as the invited speakers. Each of the three invited speakers will discuss the methods used and challenges encountered in REMS evaluation studies from their unique perspectives. Specifically, Gerald Dal Pan will discuss the scope of REMS programs in the USA with a focus on opioid analgesics, utilizing pharmacoepidemiology as a tool to assess measurements and outcomes after REMS interventions and lessons learned from assessments to date. Paul Coplan will describe objectives of opioid REMS programs and the considerations in their implementation and evaluation, and Stephan Lanes will provide an example of REMS evaluation using electronic pharmacy claims to survey patients. Following the individual presentations, the invited speakers will gather on stage for an open discussion with the audience about the presentations, and the moderator will summarize key conclusions and outstanding problems.

428. Association between Exposure to Acid-suppressing Drugs during Pregnancy and Asthma in Childhood

Lucia Cea Soriano,[1] Sonia Hernández-Díaz,[2] Saga Johansson,[3] Péter Nagy,[3] Luis A García-Rodríguez.[1] *[1]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain; [2]Harvard School of Public Health, Boston, MA, USA; [3]AstraZeneca R&D, Mölndal, Sweden.*

Background: Recent studies have suggested a link between use of acid-suppressing drugs during pregnancy and development of asthma in childhood.

Objectives: The aim of this study was to evaluate whether prenatal exposure to acid-suppressing drugs is associated with an increased risk of asthma in children.

Methods: We used The Health Improvement Network database to identify completed pregnancies during 1996–2010 in women aged 18–45 years. Pregnancies were linked to infants using family identification numbers and dates of birth. A cohort of infants exposed to proton pump inhibitors (PPIs) and/or histamine H2-receptor antagonists (H2RAs) prenatally was compared with an unexposed cohort matched for maternal age and date of last menstrual period (same quarter/year). Infants were followed up from the age of 1 year until their first recorded diagnosis of asthma, death, their sixth birthday, or end of follow-up (31 December 2011). Cox proportional hazards models were employed to estimate the rate ratio (RR) of asthma associated with maternal use of acid-suppressing drugs during pregnancy and with paternal use of these agents in the time frame corresponding to pregnancy.

Results: Compared with non-exposed infants, the crude RR for asthma in exposed infants was 1.13 (95% confidence interval: 0.89–1.44) for PPIs and 1.61 (1.36–1.91) for H2RAs. With adjustment for maternal comorbidities and co-medications, the RRs were 1.03 (0.76–1.40) for PPIs and 1.32 (1.05–1.64) for H2RAs. In infants whose mothers had prescriptions in all trimesters of pregnancy, the crude RR was 1.44 (0.74–2.77) for PPIs and 1.72 (0.89–3.33) for H2RAs; corresponding adjusted RRs were 0.73 (0.23–2.31) and 1.26 (0.51–3.08). Paternal use of PPIs or H2RAs at any time during pregnancy was associated with a crude RR of asthma in infants of 0.94 (0.55–1.60) and 1.64 (0.73–3.67), respectively.

Conclusions: Prenatal exposure to PPIs or H2RAs did not significantly increase the risk of asthma in childhood. Reductions in RR estimates with further adjustment support potential confounding because of shared familial genetic and environmental factors.

429. Oral Fluconazole in Pregnancy and Risk of Fetal Death

Ditte Mølgaard-Nielsen, Henrik Svanström, Mads Melbye, Anders Hviid, Björn Pasternak. *Department of Epidemiology Research, Statens Serum Institut, Copenhagen S, Denmark.*

Background: Azole antifungal agents are used to treat vaginal candidiasis during pregnancy. While topical formulations are considered safe and first-line treatment in pregnant women, oral formulation of fluconazole is used in certain cases despite limited safety information on the risk of fetal death.

Objectives: The aim of this study was to investigate the risk of fetal death associated with the use of oral fluconazole in pregnancy.

Methods: A register-based cohort study of 1 245 690 pregnancies in Denmark, 1997–2011, was carried out. Fluconazole-exposed pregnancies were matched with unexposed pregnancies (1:4 ratio) on gestational age, maternal age, calendar year, and propensity score. In addition, pregnancies exposed to topical azole antifungal agents were also used as a comparator group. The main outcome measures were hazard ratios of spontaneous abortion and stillbirth estimated with Cox proportional hazards regression.

Results: Oral fluconazole exposure was associated with increased risk of spontaneous abortion (126 [4.9%] cases in 2553 exposed pregnancies and 500 [4.9%] cases in 10 193 unexposed pregnancies; hazard ratio, 1.45; 95% confidence interval [CI], 1.20 to 1.76) and stillbirth (15 [0.4%] cases in 3906 exposed pregnancies and 46 [0.3%] cases in 15 605 unexposed pregnancies; hazard ratio, 1.65; 95%CI, 0.92 to 2.94). The risk of spontaneous abortion was similar ($p = 0.85$) with fluconazole doses of 150–300 mg (hazard ratio, 1.44; 95%CI, 1.18 to 1.76) and 350–5600 mg (hazard ratio, 1.54; 95% CI, 0.83 to 2.85), and oral fluconazole compared with topical azole antifungal agents was also associated with increased risk (hazard ratio, 1.87; 95% CI, 1.42 to 2.46).

Conclusions: Fluconazole exposure in pregnancy was associated with an increased risk of fetal death, but the risk did not change according to lower and higher dose. The risk was still present when comparing with topical treatment speaking against apparent confounding by indication. However, confounding by severity of vaginal candidiasis and unmeasured confounders cannot be discounted as an explanation for these findings. While these findings should be taken seriously, they need to be confirmed in independent studies before any potential changes to prescribing practice are implemented.

430. Maternal Use of Specific Selective Serotonin-reuptake Inhibitors in Early Pregnancy and the Risk of Birth Defects

Jennifer N Lind,[1,2] Jennita Reefhuis,[1] Jan M Friedman,[3] Carol Louik,[4] Tiffany Riehle-Colarusso,[1] Margaret A Honein.[1] *[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA; [2]United States Public Health Service Commissioned Corps, Atlanta, GA, USA; [3]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada; [4]Slone Epidemiology Group, Boston University, Boston, MA, USA.*

Background: Selective serotonin-reuptake inhibitors (SSRIs) are widely used to treat depression. Possible associations between SSRI use in early pregnancy and birth defects have been reported.

Objectives: The aim of this study was to assess associations between specific SSRI use in early pregnancy and the risk for specific birth defects that have not been previously evaluated in the National Birth Defects Prevention Study (NBDPS).

Methods: We analyzed NBDPS data for births in the period from 1997 to 2009. Women who reported any use of citalopram, escitalopram, fluoxetine, paroxetine, or sertraline in the period from 1 month before to 3 months after conception were considered exposed. Defects included isolated (i.e., affecting only one organ system) non-heart defects, simple (i.e., anatomically discrete), isolated congenital heart defects (CHDs), and common, uncomplicated combinations of CHDs, with at least four exposed cases. Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were estimated using multivariable logistic regression, adjusting for maternal age, race/

ethnicity, income, smoking, pre-pregnancy obesity, and parity.

Results: Results among 51 comparisons with 10 significant positive associations were as follows: citalopram and diaphragmatic hernia (aOR 3.5;95% CI 1.3, 9.1); fluoxetine and aortic stenosis (aOR 2.8;95%CI 1.3, 6.2), coarctation of the aorta (aOR 2.1;95%CI 1.0, 4.5), and pulmonary valve stenosis (PVS) (aOR 2.7;95%CI 1.5, 4.7); paroxetine and total anomalous pulmonary venous return (aOR 4.5;95%CI 1.6, 12.7), PVS in combination with atrial septal defect (ASD) (aOR 4.3;95%CI 1.5, 12.3), and ventricular septal defect (VSD) in combination with ASD (aOR 2.4;95%CI 1.0, 5.8); and sertraline and glaucoma/anterior chamber defects (aOR 4.0;95%CI 1.6, 10.1), PVS (aOR 1.9;95%CI 1.1, 3.1), and PVS in combination with VSD (aOR 4.2;95%CI 1.8, 9.8).

Conclusions: All SSRIs evaluated except escitalopram were associated with at least one major birth defect. These results support the need for evidence-based guidance for healthcare providers to select the safest options for SSRI use before and during early pregnancy to minimize the risk of major birth defects while providing adequate maternal treatment.

431. Maternal Use of Varenicline and Risk of Congenital Malformations

Morten Olsen,[1] Kenneth R Petronis,[2] Trine Frøslev,[1] Lars Pedersen,[1] Vera Ehrenstein,[1] Jingping Mo,[2] Fredrik Granath,[3] Helle Kieler,[3] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Epidemiology, Pfizer, Inc., NY, USA; [3]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden.*

Background: Smoking during pregnancy is associated with a variety of adverse birth outcomes. Varenicline is indicated for smoking cessation in adults. As with most prescription drugs, the human teratogenic potential of varenicline is unknown.

Objectives: The aim of this study was to estimate the prevalence of congenital malformations among infants exposed and not exposed to varenicline *in utero*.

Methods: The Danish and Swedish medical birth registries were used to identify all live-born infants born after 1 May 2007 and conceived after 1 December 2006, the date when varenicline first became available in the two countries. This interim look included infants born between 1 May 2007 and 31 December 2011. All infants were followed up for congenital malformations until their first birthday. Data on maternal varenicline use and congenital malformations in offspring were collected from nationwide registries of dispensed prescriptions and hospital admissions.

We defined as varenicline-exposed those infants born to mothers with at least one prescription for varenicline redeemed immediately before pregnancy to date of birth. Infants not exposed to varenicline at any time during pregnancy were divided into two comparison groups, smoking-exposed and smoking-unexposed, based on maternal smoking status self-reported at the first antenatal care visit. Chromosomal abnormalities were not included in the analysis.

Results: Eleven (4.3%) of the 254 varenicline-exposed infants had malformations: five affected the circulatory system (2.0%), two affected the digestive system (0.8%), two affected the urinary system (0.8%), and two affected the limbs (0.8%). Among varenicline-unexposed infants, 2753 (4.2%) of the 65 296 smoking-exposed and 27 270 (4.2%) of the 656 139 smoking-unexposed had malformations; the distribution of organ specific malformations was similar in the varenicline-exposed infants, the smoking-exposed comparison group, and the smoking-unexposed comparison group.

Conclusions: Based on this interim look at the study data, the prevalence of malformations among varenicline-exposed infants did not appear to be higher than among varenicline-unexposed infants.

432. The Teratogenic Risk of Antiepileptic Drugs in Pregnancy

Shuk-Li Collings,[1] Irwin Nazareth,[1] Mary Thompson,[2] Irene Petersen.[1] *[1]Primary Care & Population Health, University College London, London, UK; [2]Cegedim Strategic Data Medical Research UK, London, UK.*

Background: Antiepileptic drugs (AEDs) are prescribed to one in 200 pregnant women in the UK. However, there are concerns over the risk of major congenital malformations (MCMs) posed by AEDs. Information on drug-specific risks of commonly used AEDs is lacking, but it is essential for informing treatment decisions in women.

Objectives: The aim of this study was to estimate the relative risks of MCMs or perinatal death for common AED regimens in pregnancy.

Methods: A population-based retrospective cohort study of women prescribed AEDs prior to pregnancy was performed using UK primary care data from The Health Improvement Network. Women were aged 13–55 years, with a pregnancy delivered between 1994 and 2012. Women were categorised into groups according to whether or not they were prescribed AEDs in the first trimester and, if so, which AED. The AEDs of interest were lamotrigine monotherapy (MT), carbamazepine MT and sodium valproate MT and polytherapy (PT). Medical records and free text information of the mother and/or the child were searched for an MCM or perinatal death recorded from 20 weeks gestation up to 1 year after birth. Pairwise comparisons of risk were made using Poisson regression, adjusted for year of delivery, mother's age, level of social deprivation and indication for AEDs.

Results: A total of 1633 women were receiving AEDs prior to pregnancy. In the first trimester, 234 (14%) received no further prescriptions, 227 (14%) received sodium valproate MT, 83 (5%) sodium PT, 361 (22%) carbamazepine MT and 334 (21%) lamotrigine MT. Other AEDs or combinations of AEDs were prescribed to the remaining 394 (24%) women. Children of mothers prescribed sodium valproate PT were three times more likely to have an MCM or suffer perinatal death compared with those prescribed sodium valproate MT (aIRR 3.47, 95%CI 1.32–9.12) and five times more likely than those prescribed lamotrigine MT (aIRR 5.32, 95%CI 1.78–15.89). There was no evidence of difference in risk found for all other pairwise comparisons.

Conclusions: Most women continue to receive AED prescriptions in the first trimester of pregnancy. Sodium valproate PT is associated with an increased risk of MCMs in comparison with sodium valproate MT and lamotrigine MT.

433. Patterns of Anti-epileptic Drug (AED) Use during Pregnancy in the Mini-Sentinel Database (MSDD) among Women Delivering a Liveborn Infant

Marilyn R Pitts,[1] Katrina Mott,[1] Marsha E Reichman,[1] Carrie Ceresa,[1] Susan E Andrade,[2] Caren Kieswetter,[1] Sengwee Toh,[3] Monika Houstoun,[1] Katherine Haffenreffer.[3] *[1]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [2]Meyers Primary Care Institute, Worcester, MA, USA; [3]Harvard Pilgrim Health Care Institute, Boston, MA, USA.*

Background: In the USA, ~25 000 infants annually are born to mothers with seizure disorders. Seizures during pregnancy are associated with an increased risk of adverse maternal and fetal/neonatal outcomes. Understanding the patterns of AED use during pregnancy may help inform decisions to minimize AED-associated congenital malformations.

Objectives: This study describes patterns of AED use in the MSDD among pregnant women in the USA delivering a liveborn infant.

Methods: An analytic tool designed to assess drug use in the MSDD among women delivering a liveborn infant determined patterns of AED use in this population from 2001 to 2012. Diagnosis and procedure codes were used to calculate the estimated pregnancy start date and trimesters, based on date of delivery. Exposure to AEDs was determined by outpatient dispensing data. Medications of interest included all AEDs, but a targeted analysis focused on the more commonly used benzodiazepines, lamotrigine, gabapentin, topiramate, and valproic acid and its derivatives. All 18 Mini-Sentinel data partners contributed to this analysis.

Results: The analytic tool identified ~1.7 million pregnancies that resulted in live births, of which 2.1% had exposure to an AED at any time during the pregnancy. Use of AEDs decreased with advancing gestational age by trimester. Specifically, 1.9% of pregnancies were exposed during the first trimester, whereas 0.7% were exposed during the third. The most commonly used AEDs were benzodiazepines (0.9% in the first trimester and 0.2% in the third trimester). Less frequently used were lamotrigine, topiramate, and gabapentin (0.3%, 0.2%, and 0.2%), respectively, in the first trimester. Among the AEDs of special interest, valproic acid and its derivatives were the least used throughout pregnancy (0.1% or less).

Conclusions: The reason for the observed decrease in AED use during pregnancy is unclear, although current obstetric guidance in this area is to employ monotherapy with an agent other than valproic acid. This observation warrants further investigation, given potential adverse consequences of

uncontrolled or under-controlled seizure disorder during pregnancy.

434. Antidepressant, Especially SSRI Use, during Pregnancy and the Risk of Autism Spectrum Disorder: A Meta-analysis

Takoua Boukhris,[1] Flory Muanda-Tsobo,[1] Anick Bérard.[1,2] *[1]University of Montreal, Faculty of Pharmacy, Montreal, QC, Canada; [2]Research Center, CHU Sainte-Justine, Montreal, QC, Canada.*

Background: At present, few have investigated the effect of antidepressant use during pregnancy on the risk of autism spectrum disorders (ASD). Nevertheless, findings are controversial.

Objectives: Hence, the aim of this meta-analysis was to quantify the association between antidepressant use during pregnancy and the risk of ASD, combining all published study results.

Methods: We conducted a review of the literature search and meta-analysis of observational epidemiological studies. We searched for English and French language peer-review articles in EMBASE and MEDLINE from 1990 to January 2015. All studies had to have a comparator group. Combined estimates were calculated using DerSimonian and Laird's random effects meta-analysis model; heterogeneity was tested with I-squared statistic, and publication bias was assessed using Begg's funnel plot.

Results: We identified eight relevant published studies that have investigated the association between antidepressants use during pregnancy and the risk of ASD (four case–control studies, three cohort studies, and 1 nested case–control study). Five studies showed an increased risk of ASD associated with gestational use of antidepressants; seven studies showed that *in-utero* use of SSRIs was associated with an increase in risk of ASD. Considering all published studies, the combined estimate for the overall use of antidepressants during pregnancy was 1.56 (95%CI: 1.20–2.04) and for SSRIs specifically, 1.58 (95%CI: 1.27–1.95).

Conclusions: This meta-analysis showed that exposure to antidepressants during pregnancy, more specifically SSRI as a class, is associated with an increased risk of ASD. More research is needed to assess the impact of specific types of antidepressants as well as dosage.

435. Asthma Medicine Prescribing Before, During and After Pregnancy: A Study in 7 European Regions

Rachel Charlton,[1] Anna Pierini,[2] Kari Klungsøyr,[3,4] Amanda Neville,[5] Sue Jordan,[6] Lolkje de Jong-van den Berg,[7] Daniel Thayer,[6] H Jens Bos,[7] Aurora Puccini,[8] Anna Hansen,[9] Rosa Gini,[10] Anders Engeland,[3,4] Anne-Marie Nybo Andersen,[11] Helen Dolk,[12] Ester Garne.[9] *[1]University of Bath, Bath, UK; [2]Institute of Clinical Physiology - National Research Council (IFC-CNR), Pisa, Italy; [3]Medical Birth Registry of Norway, The Norwegian Institute of Public Health, Norway; [4]University of Bergen, Bergen, Norway; [5](IMER) Emilia Romagna Birth Registry, Ferrara, Italy; [6]Swansea University, Swansea, UK; [7]University of Groningen, Groningen, The Netherlands; [8]Emilia Romagna Region Health Authority, Bologna, Italy; [9]Hospital Lillebaelt, Kolding, Denmark; [10]The Regional Agency for Public Health of Tuscany, Florence, Italy; [11]University of Copenhagen, Copenhagen, Denmark; [12]University of Ulster, Belfast, UK.*

Background: The prevalence of asthma during pregnancy has been estimated at 4–8% in Europe, making it one of the most common, potentially serious, medical complications in pregnancy. To achieve good disease control, pregnant women and those considering becoming pregnant are generally recommended to continue taking their asthma medicines.

Objectives: The aim of this study was to explore asthma medicine prescribing patterns during and surrounding pregnancy, in seven European electronic healthcare databases.

Methods: A common protocol was implemented across databases in Denmark, Norway, the Netherlands, Italy (Emilia Romagna/Tuscany), Wales and the Clinical Practice Research Datalink, representing the rest of the UK. Women with a pregnancy starting and ending between 2004 and 2010, which ended in a delivery, were identified. Asthma medicine prescriptions issued (UK) or dispensed (non-UK) during pregnancy and/or the year before and after pregnancy were identified. Prescribing patterns were analysed and compared between databases and over calendar time.

Results: In total, 1 165 435 deliveries were identified. The prevalence of asthma medicine prescribing during pregnancy was highest in Wales and the rest of the UK (9.4% CI95 9.1–9.6 and 9.4% CI95 9.3–9.6,

respectively) and lowest in the Norwegian database (3.7% CI95 3.7–3.8). In the year before pregnancy, the prevalence of prescribing remained constant in all regions. Prescribing then peaked during the second trimester of pregnancy and was at its lowest during the 3 months following delivery. During pregnancy, prescribing of long-acting beta-2-agonists declined in Norway, the Netherlands and Italy. Differences were observed in the specific products most commonly prescribed; however, inhaled beta-2-agonists and inhaled corticosteroids were the most popular regimens in all regions. During the 7-year study period, there were only small changes in asthma medicine prescribing patterns.

Conclusions: Differences were found in the prevalence of prescribing of asthma medicines during and surrounding pregnancy and the specific products prescribed, but no major differences were observed in the therapeutic regimens prescribed in general.

436. Insulin Analogues in Pregnancy and Specific Congenital Anomalies: A Literature Review

Josta de Jong,[1] Ester Garne,[2] Ewa Wender-Ozegowska,[3] Margery Morgan,[4] Lolkje TW de Jong-van den Berg,[1] Hao Wang.[1] *[1]Pharmacoepidemiology and Pharmacoeconomics, University of Groningen, Groningen, The Netherlands; [2]Paediatric Department, Hospital Lillebaelt, Kolding, Denmark; [3]Dept. of Obstetrics and Women's Diseases, Poznan University of Medical Sciences, Poznan, Poland; [4]Congenital Anomaly Register and Information Service for Wales, Singleton Hospital, Swansea, UK.*

Background: Insulin analogues are now commonly used in diabetic pregnant women. It is therefore important to know whether exposure to insulin analogues in pregnancy is associated with any higher risk of specific congenital anomalies in the offspring compared with exposure to human insulin.

Objectives: The aim of this study was to combine the results of different studies to look for any increased risk of specific congenital anomalies among fetuses exposed to insulin analogues.

Methods: We performed a literature search for studies of pregnant women with pregestational diabetes exposed to insulin analogues in the first trimester and detailed information on specific congenital anomalies. The studies were analyzed to compare the congenital anomaly rate of infants in insulin analogue-exposed (lispro, aspart, glargine, or detemir) pregnancies with the rate in human insulin-exposed pregnancies. We compared the prevalence of specific major malformations, by reclassification according to the congenital anomaly subgroups of EUROCAT (European Surveillance of Congenital Anomalies) between pregnancies exposed to insulin analogues and human insulin. We used the chi-squared test for this comparison, and a p value <0.05 was considered as statistical significant.

Results: We found 32 studies: 2 randomized controlled trials, 16 cohort studies, and 14 observational studies of insulin analogue-exposed pregnancies. No significant difference was found in the anomaly rate among fetuses exposed to lispro (4.60 vs 5.23%; $p=0.57$), aspart (3.80 vs 4.33%; $p=0.96$), glargine (2.81 vs 3.84%; $p=0.44$), and detemir (3.47 vs 3.80%; $p=1$) compared with human insulin. The prevalence of specific congenital anomaly subgroups was not significantly higher in insulin analogue-exposed fetuses compared with human insulin-exposed fetuses.

Conclusions: No indication of increased risk of specific congenital anomalies were found among offspring of women with pregestational diabetes exposed to insulin analogues in the first trimester of pregnancy compared with those exposed to human insulin.

437. Use of Insulin Analogs in Pregestational Diabetes and Risk of Congenital Anomalies

Hao Wang,[1] Ewa Wender-Ozegowska,[2] Ester Garne,[3] Margery Morgan,[4] Maria Loane,[5] Anna Materna-Kiryluk,[2] Awi Wiesel,[6] Sue Jordan,[7] Miriam Gatt,[8] Guy Thys,[9] Vera Nelen,[9] Marian Bakker,[10] Hermien de Walle,[10] Lolkje de Jong-van den Berg.[1] *[1]University of Groningen, Groningen, The Netherlands; [2]Poznan University of Medical Sciences, Poznan, Poland; [3]Lillebaelt Hospital, Kolding, Denmark; [4]Singleton Hospital, Swansea, UK; [5]University of Ulster, Ulster, UK; [6]Johannes Gutenberg Universitat, Mainz, Germany; [7]Swansea University, Swansea, UK; [8]Department of Health Information and Research, Malta; [9]Provinciaal Instituut voor Hygiene, Antwerp, Belgium;[10]University Medical Centre Groningen, Groningen, The Netherlands.*

Background: The use of insulin analogs in pregnancy is increasing, but information on teratogenic risks is lacking. Available studies on insulin analogs during pregnancy are not sufficiently powered to evaluate the risk of specific major malformations.

Objectives: The aim of this study was to evaluate the risk of major congenital anomalies associated with insulin analogs use in women with pregestational diabetes.

Methods: A population-based cohort of pregestational diabetic pregnancies was established retrospectively from seven European regions covered by EUROCAT congenital anomaly registries. Major congenital malformations were defined according the EUROCAT classification.

Results: A total of 1877 births to women with pregestational diabetes were enrolled in the study during 1996–2012. During the first trimester, 870 births (46.3%) were exposed to only human insulin, 397 births (21.2%) to only insulin analogs, and 394 births (20.1%) to both human insulin and insulin analogs. The proportion of still birth and spontaneous abortion (4.0%) is higher among only insulin analog group compared with only human insulin group (1.4%). Overall, 132 births (7.0%) with major congenital malformation were detected, of which seven were chromosomal. The prevalence of major congenital anomalies in births exposed to only insulin analogs (3.8%) during the first trimester was significantly lower than those exposed to only human insulin (8.6%); relative risk = 0.42 (95%CI 0.24–0.73). This is largely due to the decreased prevalence of non-chromosomal congenital heart defects (CHD): relative risk = 0.18 (95%CI 0.05–0.58). The decreased prevalence remained after adjusting for glycemic control, planned pregnancy, and region. The prevalence of non-CHD congenital anomalies among births exposed to only insulin analogs in the first trimester (3.0%) was lower than those exposed to only human insulin (4.0%), but not statistically significant.

Conclusions: This study shows that first trimester exposure to insulin analogs did not increase the risk of congenital anomalies compared with exposure to human insulin. The decrease risk of congenital anomalies was driven by CHDs. The higher risk of fetal death in relation to insulin analogs warranted further investigation.

438. Patterns of Antidiabetic Agent Use During Pregnancy among Women Delivering a Liveborn Infant in the Mini-Sentinel Database (MSDD)

Katrina Mott,[1] Marsha E Reichman,[1] Darren Toh,[2] Monika Houstoun,[1] Marilyn Pitts,[1] Caren Kieswetter,[1] Carrie Ceresa,[1] Katherine Haffenreffer,[2] Susan E Andrade.[3] *[1]U.S. Food and Drug Administration, Silver Spring, MD, USA; [2]Deparment of Population Medicine, Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, MA, USA; [3]Meyers Primary Care Institute, Worcester, MA, USA.*

Background: An estimated 9% of pregnant women have pre-existing diabetes mellitus or develop gestational diabetes, which may require drug therapy during pregnancy. Utilization of antidiabetic agents (ADA) during pregnancy is particularly important in light of new drug development and updated diagnostic recommendations.

Objectives: This study describes patterns of ADA use among pregnant women delivering a liveborn infant in the MSDD.

Methods: An analytic tool designed to assess drug utilization among women delivering a liveborn infant in the MSDD was used to determine patterns of ADA use in this population from 2001 to 2012. An algorithm of diagnosis and procedure codes estimated pregnancy start date and trimesters based on date of delivery, and matched pregnant women, on age, and enrollment criteria, to non-pregnant women. Drug exposure was also assessed in a subset of pregnant women with pre-existing diabetes. Exposure to ADAs was determined by outpatient pharmacy dispensing data. Medications of interest included alpha-glucosidase inhibitors, pramlintide, metformin, DPP-4 inhibitors, GLP-1 receptor antagonists, meglitinide analogs, sulfonylureas, TZDs, and insulin. All 18 Mini-Sentinel data partners contributed to this analysis.

Results: The analysis identified over 1.6 million live birth pregnancies, of which 4.3% ($n = 71\,445$) had exposure to an ADA at any time during pregnancy, compared with 2.0% of pregnancies that had ADA exposure in the 90 days prior to pregnancy. The most commonly used ADA products during pregnancy were insulin (1.8%), metformin (1.7%), and glyburide (1.4%). Compared with the first trimester, use in the third trimester of metformin decreased (1.5% vs. 0.5%), while used of insulin (0.7% vs. 1.8%) and glyburide (0.1% vs. 1.3%) increased. During the third trimester, 3.3% of pregnancies were exposed to an ADA. Of the pregnancies with pre-existing diabetes who received an ADA ($n = 13\,956$), 93% continued to receive an ADA during pregnancy.

Conclusions: In this large retrospective cohort of women delivering liveborn infants in the USA, 4.3%

of pregnancies were exposed to an ADA. Use of most oral ADAs during pregnancy remains low.

439. Risk of Preterm Delivery among Live Births Exposed to Anti-diabetic Agents during the First Trimester of Pregnancy

Caitlin A Knox,[1,2] Christian Hampp,[3] Babette Brumback,[4] Xiaohui Xu,[5] Richard Segal,[1] Almut G Winterstein.[1,5] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Safety and Epidemiology, HealthCore, Andover, MA, USA; [3]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA; [4]Biostatistics, University of Florida, Gainesville, FL, USA; [5]Epidemiology, University of Florida, Gainesville, FL, USA.*

Background: Pre-existing diabetes is a risk factor for preterm delivery. Research is limited to investigating the risk associated with the use of anti-diabetic agents and preterm delivery.

Objectives: The aim of this study was to assess the risk of preterm delivery in pre-existing diabetic women treated with anti-diabetic agents in the first trimester of pregnancy.

Methods: We established retrospective cohorts of women with a claim for live birth, age 12 to 55 years, with continuous Medicaid eligibility 6 months before pregnancy until delivery from 2000 to 2006 in 29 US states in the Medicaid Analytic eXtract database. Women were required to have pre-existing diabetes (≥1 inpatient or ≥2 outpatient claims with ICD-9-CM 250.XX before pregnancy), to have used an anti-diabetic agent, either monotherapy or dual-therapy, during the first trimester of pregnancy, and to have no pharmacy claims for insulin in their pre-conception period. Preterm delivery was defined as ≥1 inpatient or outpatient claim with ICD-9-CM 644.0X, 644.42, 765.0X, 765.1X, 765.20–25, or 765.27–28. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with logistic regression. We compared monotherapy anti-diabetic drugs to metformin and dual-therapy to metformin plus another anti-diabetic agent.

Results: The study cohort included 1980 deliveries with monotherapy or dual-therapy exposure in the first trimester of pregnancy. The cohort was mainly White, non-Hispanic, located in the southern region of the USA, and had a mean age of 37.1 years. Across all agents, we observed 163 (8.2%) preterm delivery within the cohort. The adjusted odds ratio of preterm delivery was 2.05 (95%CI: 1.09, 3.83) for sulfonylureas, 0.85 (95%CI: 0.36, 2.01) for thiazolidinediones, and 2.59 (95%CI: 1.61, 4.17) for insulin compared with metformin.

Conclusions: Within this analysis, the odds of preterm delivery were elevated among women exposed to sulfonylureas and insulin in the first trimester of pregnancy. Further studies are needed to explore the effect anti-diabetic agents have on the risk of preterm delivery, as well as address potential unmeasured confounders not captured within this data.

440. Risk of Preeclampsia among Live Births Exposed to Anti-diabetic Agents during the First Trimester of Pregnancy

Caitlin A Knox,[1,2] Christian Hampp,[3] Babette Brumback,[4] Xiaohui Xu,[5] Richard Segal,[1] Almut G Winterstein.[1,5] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Safety and Epidemiology, HealthCore, Andover, MA, USA; [3]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA; [4]Biostatistics, University of Florida, Gainesville, FL, USA; [5]Epidemiology, University of Florida, Gainesville, FL, USA.*

Background: Pre-existing diabetes is associated with an increased risk of preeclampsia, but the risk associated with anti-diabetic agents is unclear.

Objectives: The aim of this study was to compare the risk of preeclampsia in women with pre-existing diabetes treated with various anti-diabetic agents in the first trimester of pregnancy.

Methods: We established retrospective cohorts of women age 12 to 55 years with a claim for live birth and continuous Medicaid eligibility 6 months before pregnancy until delivery from 2000 to 2006 in 29 US states in the Medicaid Analytic eXtract database. Women were required to have pre-existing diabetes (≥1 inpatient or ≥2 outpatient claims with ICD-9-CM 250.XX before pregnancy), to have used an anti-diabetic agent, either monotherapy or dual-therapy,

during the first trimester of pregnancy, and to have no pharmacy claims for insulin during their pre-conception period. We employed time-to-event analyses to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the risk of preeclampsia. We compared monotherapy anti-diabetic drugs to metformin and dual-therapy to metformin plus another anti-diabetic agent.

Results: The study cohort had 1980 deliveries with monotherapy or dual-therapy exposure in the first trimester of pregnancy, and 6.5% had a diagnosis of preeclampsia during pregnancy. The cohort was predominantly White, non-Hispanic, located in the southern region of the USA, and had a mean age of 37.1 years. Compared with metformin, the adjusted HR for preeclampsia in women exposed to sulfonylureas was 0.61 (95%CI: 0.36, 1.04), 0.58 (95%CI: 0.32, 1.04) for thiazolidinedione, and 0.86 (95%CI: 0.56, 1.32) for insulin. Dual-therapy of metformin and thiazolidinedione had an increased adjusted HR of 1.74 (95%CI: 0.78, 3.89) when compared with metformin and sulfonylurea.

Conclusions: Although not statistically significant, we found that exposure to metformin in the first trimester of pregnancy appeared to be associated with a higher risk of preeclampsia in both monotherapy and dual-therapy combinations. Studies are needed to investigate this association further.

441. Risk of Cesarean Section Delivery among Live Births Exposed to Anti-Diabetic Agents during the First Trimester of Pregnancy

Caitlin A Knox,[1,2] Christian Hampp,[3] Babette Brumback,[4] Xiaohui Xu,[5] Richard Segal,[1] Almut G Winterstein.[1,5] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Safety and Epidemiology, HealthCore, Andover, MA, USA; [3]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA; [4]Biostatistics, University of Florida, Gainesville, FL, USA; [5]Epidemiology, University of Florida, Gainesville, FL, USA.*

Background: Diabetes mellitus is an independent risk factor for cesarean section delivery. However, there is limited information on the risk of cesarean section delivery associated with oral anti-diabetic treatment.

Objectives: The aim of this study was to assess the risk of cesarean section delivery in pre-existing diabetic women treated with anti-diabetic agents in the first trimester of pregnancy.

Methods: We established retrospective cohorts of women with a claim for live birth, age 12 to 55 years, with continuous Medicaid eligibility 6 months before pregnancy until delivery from 2000 to 2006 in 29 US states in the Medicaid Analytic eXtract database. Women were required to have pre-existing diabetes (≥1 inpatient or ≥2 outpatient claims with ICD-9-CM 250.XX before pregnancy), to have used an anti-diabetic agent, either monotherapy or dual-therapy, during the first trimester of pregnancy, and to have no pharmacy claims for insulin in their pre-conception period. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with logistic regression. We compared monotherapy anti-diabetic drugs to metformin and dual-therapy to metformin plus another anti-diabetic agent.

Results: The study cohort had 1980 deliveries with monotherapy or dual-therapy exposure in the first trimester of pregnancy, and 29.6% of deliveries occurred via cesarean section. The cohort was predominantly White, non-Hispanic, located in the southern region of the USA, and had a mean age of 37.1 years. Point estimates suggested little difference in risk for cesarean section delivery: sulfonylureas (OR 0.94, 95%CI: 0.68, 1.30), thiazolidinediones (OR 0.98, 95%CI: 0.65, 1.47), and dual therapies (OR 0.89, 95%CI: 0.49, 1.61), but the CIs were wide. In contrast, insulin showed increased odds (OR 1.41, 95%CI: 1.05, 1.89).

Conclusions: We found little difference in the odds of cesarean section delivery between sulfonylureas or thiazolidinedione when compared with metformin, whereas insulin exposure had an increased risk.

442. Sulfonamide Use during the First Trimester of Pregnancy and Risk of Selected Congenital Anomalies among Live Births

Craig Hansen,[17] Susan E Andrade,[1] Heather Freiman,[2] Sascha Dublin,[3] Katie Haffenreffer,[4] William O Cooper,[5] T Craig Cheetham,[6] Darren Toh,[4] De-Kun Li,[7] Marsha A Raebel,[8] Jennifer L Kuntz,[9] Nancy Perrin,[9] A Gabriela Rosales,[9] Shelley Carter,[10] Pamala A Pawloski,[11] Elizabeth M Maloney,[12] David J Graham,[12] Leyla Sahin,[13] Pamela E Scott,[14] John Yap,[15] Robert Davis.[16] *[1]Meyers Primary Care Institute, University of Massachusetts Medical School*

Worcester, Worcester, MA, USA; [2]Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA, USA; [3]Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA; [4]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA; [5]Departments of Pediatrics and Health Policy, Vanderbilt University School of Medicine, Nashville, TN, USA; [6]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA; [7]Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, CA, USA; [8]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA; [9]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA; [10]LCF Research, Albuquerque, NM, USA; [11]HealthPartners Institute for Education and Research, Minneapolis, MN, USA; [12]Office of Surveillance and Epidemiology, Food and Drug Administration, Silver Spring, MD, USA; [13]Office of New Drugs, Food and Drug Administration, Silver Spring, MD, USA; [14]Office of Women's Health, Food and Drug Administration, Silver Spring, MD, USA; [15]Office of Biostatistics, Food and Drug Administration, Silver Spring, MD, USA; [16]Center for Biomedical Informatics and Department of Pediatrics, University of Tennessee, Memphis, TN, USA; [17]South Australian Health and Medical Research Institute, South Australia, Australia.

Background: Sulfonamide antibacterials are widely used in pregnancy, but evidence about their safety is mixed.

Objectives: The aim of this study was to assess the association between first trimester sulfonamide exposure and risk of specific congenital malformations.

Methods: This retrospective cohort study included 1.2 million liveborn deliveries between 2001 and 2008 at 11 US health plans participating in the Medication Exposure in Pregnancy Risk Evaluation Program, which has linked health plan with birth certificate data. Deliveries to mothers with first trimester sulfonamide exposure were randomly matched 1:1 to those exposed to penicillins or cephalosporins (primary comparator) or no antibacterials (secondary comparator). We examined anomalies that in prior studies were associated with sulfonamide use: cardiovascular abnormalities, cleft lip/palate, clubfoot, neural tube defects (NTDs), and urinary tract abnormalities. Outcomes were validated by medical record review. Analyses used conditional logistic regression.

Results: There were 6688 deliveries in each exposure group included in primary analyses. Cardiovascular defects occurred in 1.6%; urinary system defects, 0.7%; clubfoot, 0.2%; and cleft lip/palate, 0.1%. NTDs were too rare for further evaluation ($n = 5$). Sulfonamide exposure was not associated with significantly elevated risks for these anomalies. The adjusted OR for cardiovascular defects was 0.94 (95%CI, 0.71–1.23) for sulfonamide exposure compared with penicillin/cephalosporin exposure. The comparable ORs were 0.83 (0.18–3.88) for cleft lip/palate and 1.08 (0.70–1.65) for urinary defects. For clubfoot, the OR was elevated but not statistically significant (OR 1.58 [0.71–3.50]). In comparison, analyses comparing sulfonamide exposure with no antibiotic use yielded estimates that were farther from the null, although still nonsignificant.

Conclusions: First trimester sulfonamide exposure was not associated with a higher risk of the congenital anomalies studied, compared with exposure to penicillins or cephalosporins. Our results highlight the need to use active comparator groups exposed to medications with the same indication to minimize confounding.

443. HAART Use during Pregnancy and the Risk of Major Congenital Malformations

Anick Bérard, Odile Sheehy, Sasha Bernatsky, Marc Boucher. *CHU Ste-Justine, Montreal, Canada; University of Montreal, Montreal, Canada; McGill University, Montreal, Canada.*

Background: The number of Canadians with HIV infections is increasing each year, and treatment with highly active antiretroviral therapy (HAART) increases life expectancy. Subsequently, we are seeing an increasing number of pregnant women on HAART. At present, however, few data exist on the risk of using HAART during pregnancy.

Objectives: The aim of this study was to quantify the risk of major congenital malformations associated with HAART use during pregnancy.

Methods: A case–control analysis was conducted within the Quebec Pregnancy Cohort during 1998–2009. To be eligible, women had to be covered by the Quebec provincial drug plan at least 12 months before and during pregnancy and have a singleton

delivery. All pregnancies meeting these eligibility criteria were considered. The unit of analysis was a pregnancy. The following HAART exposures were considered in the first trimester: protease inhibitors including darunavir, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and fixed-dose combinations. Cases of major malformations were identified in the first year of life. Univariate and multivariate generalized estimation equation models were used.

Results: Overall, 75 670 pregnancies met inclusion criteria and were considered; 0.02% of pregnancies were using HAART, and the prevalence of major malformations was 5%. Adjusting for maternal comorbidities (HIV status, hypertension, diabetes, asthma, and anxiety disorders), hospitalization and physician visits, other medication use, and socio-economic status, HAART use during the first trimester of pregnancy was increasing the risk of gastro-intestinal tract defects (OR 4.84, 95%CI 2.02, 11.56) and urogenital defects (OR 5.26, 95%CI 2.20, 12.58).

Conclusions: Use of HAART during the first trimester of pregnancy has been shown to increase the risk of GI and urogenital defects. Although HAART are used during pregnancy to decrease mother-to-child transmission, care should be taken when used during organogenesis.

444. Quality of Reporting of Malaria Trials during Pregnancy and Its Impact on the Effectiveness of Antimalarial Drug

Flory Tsobo Muanda,[1] Anick Bérard.[1] *[1]Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada; [2]Research Center, CHU Sainte-Justine, CHU Sainte-Justine, Montreal, QC, Canada.*

Background: No studies have evaluated the quality of reporting of malaria trials and its influence on the effectiveness of antimalarial drug prescribed for malaria prevention in reducing the risk of low birth weight (LBW).

Objectives: The objectives of this study were (1) to describe biases that may arise from the main components of randomised controlled trials (RCTs) and whether the introduction of Consolidated Standards of Reporting Trials (CONSORT) may influence the quality of reporting of trials; and (2) to examine the impact of bias on the effectiveness of antimalarial drugs in preventing the risk of low birth weight.

Methods: RCTs and risk of bias assessment of each study were retrieved from a previous systematic review evaluating the effectiveness of antimalarial drugs. Proportion of trials with low, high and unclear risk of bias was computed overall and individually for each domain of bias using the Cochrane risk of bias tool; the quality of reports of RCTs was compared between trials published before and after the introduction of the CONSORT. A meta-regression analysis was performed to examine whether a difference exists between treatment effect estimates in subgroup of trials having low risk of bias and high or unclear risk of bias.

Results: A total of 26 RCTs were included in this study. Most trials had overall high (69.3%) or unclear (11.5%) risk of bias. Only 5 studies out of 26 (19.2%) were classified as having a low risk of bias. The introduction of the CONSORT statement was significantly associated with an increase of proportion of trials having a low risk of bias for sequence generation (0% vs 52.3%; $p=0.04$) and allocation concealment (0%vs 57.1%; $p=0.03$). The effectiveness of antimalarial drugs used during pregnancy in reducing the risk of LBW did not significantly differ between trials having low risk of bias and trials having high or unclear risk of bias for each domain assessed by the Cochrane risk of bias tool.

Conclusions: Malaria trials conducted during pregnancy are overall poorly reported but may be improved with the use of CONSORT statement. The assessment of the influence of risk of bias in trial conducted in malaria area should be considered in meta-analysis

445. Women's Values and Preferences: Decision Making about Thromboprophylaxis in Pregnancy

Luciane C Lopes,[1] Shannon M Bates,[2] Pablo Alonso-Coello,[3] Mark Eckman,,[4] Ignacio Neumann,[11] Elie A Akl,[8] Amparo Santamaria,[7] Anne F Jacobsen,[6] Yuqing Zhang,[5] Kari A Tikkinen,[9] Shanil Ebrahim,[5] Sarah D McDonald,[10] Gordon H Guyatt.[5] *[1]Pharmaceutical Science, University of Sorocaba, Sorocaba,*

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Sao Paulo, Brazil; [2]Department of Medicine, Mcmaster University, Hamilton, ON, Canada; [3]CIBERESP-IIB Sant Pau, Iberoamerican Cochrane Centre, Barcelona, Spain; [4]Division of Internal Medicine and Center for Clinical Effectiveness, University of Cincinnati, Cincinnati, USA; [5]Departments of Medicine and Clinical Epidemiology & Biostatistics, Mcmaster University, Hamilton, ON, Canada; [6]Department of Obstetrics & Gynecology, University of Oslo, Oslo, Norway; [7]Unidad de Hemostasia y Trombosis, Hospital de la Vall d'hebron Sant Pau, Barcelona, Spain; [8]Department of Internal Medicine, American University of Beirut, Beirut, Lebanon; [9]Department of Urology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; [10]Departments of Obstetrics & Gynecology and Radiology, McMaster University, Hamilton, Canada; [11]Department of Internal Medicine, Pontificia Universidad Catolica de Chile, Santiago, Chile.

Background: The risk of pregnancy-related venous thromboembolism (VTE) is increased in women with a history of thrombosis. Although antepartum low molecular weight heparin (LMWH) prophylaxis can reduce this risk, uncertainty persists regarding the net benefit of thromboprophylaxis, and recommendations about the use of antepartum LMWH should be sensitive to pregnant women's values and preferences, which have not previously been studied.

Objectives: The aim of this study was to determine the values, preferences, and choices of women with prior VTE who were currently pregnant or might in the future become pregnant with respect to the use of antepartum LMWH prophylaxis.

Methods: Design: Cross-sectional interview study.

Setting: Seven tertiary care centers in six countries.

Participants: Women with a history of VTE who were either pregnant, planning pregnancy, or might consider pregnancy in the future.

Interventions: We provided detailed information regarding risk of VTE recurrence with and without LMWH and determined each participant's willingness to receive LMWH prophylaxis through direct choice exercises based on real-life and hypothetical scenarios, preference-elicitation for health states, and a probability trade-off exercise.

Results: Of 123 women, more women at high risk (86.4%) than those at low risk (60.0%) of recurrence ($p = 0.003$) chose to use LMWH. The median threshold reduction in VTE at which women were willing to accept use of LMWH, given a 16% risk of VTE without prophylaxis, was 3%. Women without previous experience with LMWH in comparison with those with previous experience required a smaller reduction in VTE risk to choose LMWH. Participants' evaluation of the aversiveness (disutility) of the relevant health states varied widely and was unrelated to their direct choices to use or not use LMWH.

Conclusions: Although the majority of women with a previous VTE, pregnant, or planning pregnancy choose to take LMWH during pregnancy, a minority —and in low-risk women, a large minority—do not. This highlights the need for individualized shared decision making in the clinical encounter and for guideline panels to make weak recommendations in favor of LMWH that make clear the need for shared decision making.

446. Use of Antihypertensive Drugs in Pregnancy. A Cross-sectional Study in the Lazio Region, Italy

Martina Ventura,[1] Ursula Kirchmayer,[1] Serena Donati,[2] Alice Maraschini,[2] Alessandra Marani,[3] Marta Buoncristiano,[2] Sabrina Senatore,[2] Flavia Mayer,[1] Marina Davoli.[1] *[1]Department of Epidemiology, Lazio Regional Health service, Rome, Italy; [2]National Centre for Epidemiology, Surveillance and Health Promotion, Italian National Institute of Health, Rome, Italy; [3]University "La Sapienza"Rome, Italy.*

Background: Drug consumption during pregnancy is a matter of concern, especially regarding potential teratogens. Among antihypertensives, agents acting on the renin-angiotensin system (ACEI/ARBs) are considered as potential teratogens. In pregnancy, women chronically treated with ACEI/ARBs should switch to alternative available treatments, and newly diagnosed hypertension should be treated with other antihypertensives.

Objectives: This cross-sectional study investigates the use of ACEI/ARBs during pregnancy in the Lazio region, Italy.

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Methods: All births registered in 2008–2012 in mothers aged 18–45 years, resident in Lazio, were enrolled from the delivery care registry. Pregnancy trimesters were defined using information on gestational age at birth. Mothers' drug prescriptions during pregnancy and in the year before conception were retrieved from the drug claims register. A focus on ACEI/ARBs (ATC C09) was performed by comparing prescriptions of antihypetensive drugs registered in the year before conception with those observed during pregnancy.

Results: Overall, 212 703 births were registered, referring to 189 923 women. In 80.4% of pregnancies, at least one drug was prescribed (mean 5.6), excluding vitamins and minerals.

Use of potential teratogens was generally low, and the mostly prescribed agents were ACEI/ARBs (0.5% of pregnancies). Among the 1622 cases, in which the mother was on ACEI/ARBs in the year before pregnancy, 54.4% discontinued use during pregnancy, 19.8% switched to other antihypertensives (appropriate switch), and 25.8% stayed on the same drug. Among the 2672 women treated with alternative antihypertensives in the year before, 73.5% discontinued, 24.9% stayed on the same drug, and 1.6% switched to ACEI/ARBs during pregnancy (inappropriate switch). In the group of women starting antihypertensive treatment during pregnancy ($N=4289$), only few women used ACEI/ARBs ($N=612$, 14.3%).

Conclusions: In Lazio, ACEI/ARB use during pregnancy is limited. Still, we identified a small proportion of women newly prescribed with these drugs in pregnancy and others switching from not teratogen antihypertensives to ACEI/ARBs during pregnancy.

(Study founded by Reg. Pharmacovigilance call 2011).

447. Pregnancies and Pregnancy Outcomes during Isotretinoin Treatment in Four Canadian Provinces

David Henry,[1] Colin Dormuth,[2] Brandy Winquist,[3] Shawn Bugden,[4] Robert Platt.[5] *[1]University of Toronto and the Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [2]University of British Columbia, Vancouver, BC, Canada; [3]University of Saskatchewan, Saskatoon, SK, Canada; [4]University of Manitoba, Winnipeg, MB, Canada; [5]Lady Davis Research Institute, Jewish General Hospital, Montreal, QC, Canada.*

Background: Isotretinoin (IST), a potent teratogen, is widely used to treat cystic acne. In Canada, the voluntary pregnancy prevention program (PPP) requires written informed consent, two −ve pregnancy tests before, and two reliable forms of contraception during, treatment.

Objectives: The objectives of this study were to evaluate the Canadian PPP in four Canadian provinces (BC, SK, MB and ON—population 20.7 million) and to measure oral contraceptive (OC) use prior to and during IST treatment, rates of pregnancy and pregnancy outcomes.

Methods: We identified four historical cohorts of female users of IST, aged 12–48 years, between 1996 and 2011 and created 'high specificity' and 'high sensitivity' definitions of pregnancy using ICD–9/10 codes and billing codes. We studied new courses of IST and detected pregnancies in several time windows, including during IST treatment only and up to 42 weeks after IST, in order to capture all pregnancy outcomes.

Results: 59 271 women received 102 308 courses of IST. Between 24.3% and 32.9% of women received prescriptions for OC with IST, compared with 29.0–35.9% in the previous 12 months. Using the high specificity definition, there were 186 pregnancies during IST treatment (3.1/1000 women) compared with 367 (6.2/1000 women) with the high sensitivity definition. During IST + follow-up to 42 weeks, there were 1473 pregnancies (24.9/1000 women) using the high specificity definition. Of these, 1331 (90%) terminated either spontaneously or medically. We documented 118 live births of whom 11 (9.3%) had congenital malformations. Between 1996 and 2011, pregnancy rates (high specificity) remained constant at 2–3/1000 women during IST treatment.

Conclusions: Estimated pregnancy rates varied according to the definitions used, illustrating the challenge of defining pregnancies with administrative data. The most conservative figures indicate a rate of 3 to 6/1000 women during IST treatment. Concomitant use of OC was low, no higher than in the previous 12 months. Very few pregnancies went to term. We estimate that the number of IST-exposed live births with congenital malformations in Canada is around 1/year.

448. Intranasal Triamcinolone Use during Pregnancy and the Risk of Adverse Pregnancy Outcomes

Anick Bérard, Odile Sheehy, Marie-Laure Kurzinger, Juhaeri Juhaeri. *CHU Ste-Justine, Montreal, Canada; University of Montreal, Montreal, Canada; Sanofi, R&D, Global Pharmacovigilance and Epidemiology, Paris, France; Sanofi, R&D, Global Pharmacovigilance and Epidemiology, Bridgewater, USA.*

Background: Although some intranasal corticosteroids used in the treatment of rhinitis have been studied during pregnancy, no one has specifically looked at the safety profile of gestational intranasal triamcinolone use, recently introduced over-the-counter in the USA.

Objectives: The aim of this study was to estimate the safety of intranasal triamcinolone use during pregnancy.

Methods: Register-based cohort study in Quebec, 1998–2008, was carried out. From a cohort of 289 723 pregnancies, intranasal triamcinolone-exposed, other intranasal corticosteroids-exposed, and non-exposed women were studied. Primary outcomes were major congenital malformations, spontaneous abortions, and small for gestational age (SGA) newborns. Generalized estimating equation models were used to obtain odds ratios (OR) and 95% confidence intervals (CI).

Results: There were 143 152 pregnancies included in the analyses for major congenital malformations, 153 324 in the analyses for SGA, and 289 723 for the analyses of spontaneous abortions; 318 (0.2%) pregnancies were exposed to intranasal triamcinolone during the first trimester, and 492 (0.3%) during the second or third trimesters. Adjusting for potential confounders, use of intranasal triamcinolone during the first trimester of pregnancy was not statistically significantly associated with the risk of overall congenital malformations (OR 0.88; 95% CI 0.60–1.28; 31 exposed cases) compared with non-exposure; it was, however, associated with the risk of respiratory defects (OR 2.71; 95%CI 1.11–6.64; five exposed cases). No association was found between second or third trimester exposure to intranasal triamcinolone and the risk of SGA (OR 1.06; 95%CI 0.79–1.43; 50 exposed cases). Pregnancy exposure to intranasal triamcinolone was also not statistically significantly associated with the risk of spontaneous abortions (OR 1.04; 95%CI 0.76–1.43; 50 exposed cases).

Conclusions: Maternal exposure to intranasal triamcinolone during pregnancy has not been shown to increase the risk of SGA or spontaneous abortions. It has, however, been shown to potentially increase the risk of respiratory system defects. Given that intranasal triamcinolone is available over-the-counter, replication of results is essential to rule out chance finding.

449. Calcium Channel Blockers to Prevent Preterm Labor: A Drug Utilization Study in Two French Databases

Justine Benevent,[1] Anna-belle Beau,[1] Béatrice Guyard-Boileau,[2] Caroline Delarue-Hurault,[1] Isabelle Lacroix,[1] Jean-Louis Montastruc,[1] Christine Damase-Michel.[1] *[1]Service de Pharmacologie Médicale et Clinique, Faculté de Médecine, Université Toulouse III, CHU, INSERM1027, Toulouse, France; [2]Service de Gynécologie-Obstétrique, Hôpital Paule de Viguier, Centre Hospitalier Universitaire (CHU), Toulouse, France.*

Background: As preterm labor is the leading cause of neonatal morbidity and mortality, administration of tocolytic agents is necessary to delay delivery. Although calcium channel blockers (CCB) are not approved in obstetrics, their efficacy was established to treat preterm labor. In comparison with β2-mimetics drugs, CCB would have less adverse effects. Although they have not been demonstrated to be effective in such a use, CCB seem to be also prescribed to outpatients in an attempt to prevent the onset of preterm contractions.

Objectives: The aim of this study was to describe CCB prescription patterns during pregnancy, used as a maintenance therapy to prevent preterm labor, and the outcomes of these pregnancies.

Methods: An observational drug utilization study was performed using two French databases. The first is the French general beneficiary sample database (EGB) (a representative sample of the French population covered by the national healthcare insurance system, linked to the national hospital-discharge summary database). To go further with the results and to study the potential effects of CCB on exposed children, a complementary

database was used, EFEMERIS, including prescribed and dispensed reimbursed drugs in Haute-Garonne during pregnancy and pregnancy outcomes. Women who delivered between 1 January 2012 and 31 December 2012 and who received at least one CCB drug during the second and/or third trimester of pregnancy have been included.

Results: Between 2% and 3% of the pregnant women were exposed to CCB. Exposure mostly occurred during the third trimester of pregnancy. The slow release formulation of nifedipine and nicardipine was the most prescribed CCB. CCB were mostly prescribed by general practitioners and obstetricians. In EFEMERIS, nearly 20% of the infants were born preterm. The mean birthweight was 3015 ± 569 g, and 11% of children had neonatal pathologies during the first week of life.

Conclusions: A wide ambulatory prescription of CCB to pregnant women on late pregnancy was observed. These results are a first step to a comparative study evaluating pregnancy outcomes and children health of mothers exposed to CCB.

450. Risk Factors Associated with Early Intrauterine Device Insertion after Delivery

Efe Eworuke, David G Moeny. *Division of Epidemiology II, Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA.*

Background: To reduce the risk of uterine perforation associated with intrauterine device (IUD) insertion, the current product labeling recommends delaying IUD insertion until 6 weeks after delivery.

Objectives: The aim of this study was to examine the association between selected patient characteristics and IUD insertion at <6 weeks post-delivery (early IUD insertion).

Methods: We identified women with at least one medical procedure claim for IUD insertion after delivery (vaginal or cesarean) in the IMS Health LifeLinkTM database from 2001 to 2013 and classified the device type as levonorgestrel (LNG), copper (Cu), or unknown. Continuous eligibility was required from the date of delivery to the date of the first insertion to assure capture of medical services during the postpartum interval. Multiple deliveries were included if there was a minimum of 270 days in between deliveries. Using random effects logistic regression, we examined the association between early IUD insertion and selected patient characteristics.

Results: Of the 515 977 insertions identified, 156 223 (30.3%) met the inclusion criteria. Most were LNG IUDs (66.0%) with most insertions occurring between 6 and 14 weeks after delivery. Cu IUDs were associated with early insertion, compared with LNG IUDs (odds ratio (OR):1.09 (95% confidence interval [CI]:1.02–1.18)).

Younger (12–15 years) [OR:2.61 (CI:1.59–4.24)] and older (16–20 years) [OR:1.19: (CI:1.09–1.29)] adolescent girls were more likely to receive an early IUD insertion compared with women of prime age (21–34 years). Using the same reference group, women in the early (35–39 years) [OR:0.72 (CI:0.65–0.80)] and late advanced maternal age (40–60 years) [OR:0.68 (CI:0.53–0.87)] were less likely to have an early IUD insertion. Women in the southern region were also more likely to have an early insertion compared with the western region [OR:1.24 (CI:1.15–1.34)].

Conclusions: Younger women are more likely to receive IUD insertions earlier than 6 weeks post-delivery, potentially exposing more women to the risk of perforation. Future studies are needed to examine the relationship between age, timing of insertion, and the risk of perforation.

451. Periconceptional Benzodiazepine Use and the Risk for Birth Defects: Data from the National Birth Defects Prevention Study

Sarah Tinker,[1] Jennita Reefhuis,[1] Cheryl Broussard,[1] Suzanne Gilboa,[1] Rebecca Bitsko,[1] Martha Werler,[2] Allen Mitchell.[2] *[1]NCBDDD, CDC, Atlanta, GA, USA; [2]Schools of Public Health and Medicine, Boston University, Boston, MA, USA.*

Background: Benzodiazepine medications can be used to treat anxiety, a common condition affecting 15% of women of childbearing age in the United States. Studies have shown conflicting results on the association between benzodiazepines and birth defects.

Objectives: The aim of this study was to assess the association between benzodiazepines and birth defects.

Methods: We assessed whether periconceptional use of benzodiazepines was associated with an increased risk for selected birth defects using data from the population-based, multisite National Birth Defects Prevention Study. Logistic regression was used to estimate odds ratios for defect categories for which there were at least three exposed cases.

Results: Benzodiazepine use during the periconceptional period (month before to 3 months after conception) was reported by 0.7% (71/10 136) of mothers of control infants (liveborn without major birth defects). Alprazolam accounted for approximately half of the benzodiazepine exposures. The prevalence of use of benzodiazepines decreased dramatically between the first and third month of pregnancy, corresponding to the timing of pregnancy recognition. Periconceptional alprazolam use was associated with esophageal atresia (crude odds ratio [cOR]: 3.6; 95% confidence interval [CI]: 1.7, 7.7) and hypospadias (cOR: 0.3; 95%CI: 0.1, 0.9); clonazepam use was associated with anotia/microtia (cOR: 3.9; 95%CI: 1.1, 13.8) and tetralogy of Fallot (cOR: 2.7; 95%CI: 1.1, 6.6); and lorazepam use was associated with pulmonary valve stenosis (cOR: 4.1; 95% CI: 1.2, 14.2), coarctation of the aorta (cOR: 4.4; 95%CI: 1.1, 16.9), and gastroschisis (cOR: 4.9; 95% CI: 1.4, 16.6). Individual adjustment for maternal age, race/ethnicity, education, and smoking status did not affect OR estimates, with the exception of gastroschisis, for which adjustment for age tended to strengthen associations.

Conclusions: These results warrant additional study. Future analyses using empirical Bayesian methods will address potential confounding and data instability due to small sample size.

452. Psychotropic Medications in Combination Prior to Pregnancy: A UK Population-based Study

Rachel L McCrea,[1] Irwin Nazareth,[1] David PJ Osborn,[2] Stephen JW Evans,[3] Irene Petersen.[1] *[1]Department of Primary Care and Population Health, University College London, London, UK; [2]Division of Psychiatry, University College London, London, UK; [3]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK.*

Background: Up to now, most pharmacoepidemiology studies have focussed on exposure to a single type of drug. In this study, we focus on exposure to multiple psychotropic drugs prior to pregnancy.

Objectives: The objectives of this study were (1) to explore how antidepressants and antipsychotics are prescribed in combination prior to pregnancy; (2) to compare the characteristics of women prescribed antipsychotics or antidepressants in combination with those prescribed the drug alone; and (3) to assess whether taking these drugs in combination or alone is associated with discontinuation in pregnancy.

Methods: We identified women prescribed antipsychotics or antidepressants in the 6–3 months before pregnancy using data from The Health Improvement Network (THIN) primary care database. We quantified the most common combinations of drugs prescribed before pregnancy including antidepressants, antipsychotics, antiepileptics, lithium, anxiolytics and hypnotics. We compared the characteristics of those prescribed antidepressants or antipsychotics alone to those prescribed in combination with other drugs and used the Kaplan–Meier plots to compare time with last prescription in the two groups.

Results: Among women prescribed antidepressants in the 6–3 months before pregnancy, 88% received the antidepressant alone. However, among women prescribed antipsychotics, only 29% received the drug alone. Women prescribed antidepressants in combination with other drugs were older, more likely to have a diagnosis of a severe mental illness and more likely to come from a deprived background than those prescribed antidepressants alone. Women prescribed antipsychotics in combination with other drugs did not differ on age or deprivation but were less likely to have a severe mental illness diagnosis than those prescribed antipsychotics alone.

Women prescribed antidepressants alone were more likely to discontinue their medication during pregnancy than those prescribed antidepressants in combination; for antipsychotics, there was limited difference between the two groups.

Conclusions: Antipsychotic drugs are frequently prescribed alongside other drugs prior to pregnancy. This

has implications for how we evaluate the risks of taking these medications in pregnancy.

453. Use of Folic Acid and Antidepressants during Pregnancy and Child Language Development

Marte Handal,[1] Svetlana Skurtveit,[1] Christine Roth,[2] Sonia Hernandez-Diaz,[3] Randi Selmer.[1] *[1]Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo, Norway; [2]Nic Waals Institute, Lovisenberg Deaconess Hospital, Oslo, Norway; [3]Epidemiology, Harvard School of Public Health, Boston, USA.*

Background: Folic acid supplementation has been suggested to improve neurodevelopment, while selective serotonin reuptake inhibitors (SSRIs) have been associated with delayed language development. The effect of concomitant use of folic acid and SSRI by pregnant women on child neurodevelopment is unknown.

Objectives: The aim of this study was to determine the effect of simultaneous use of folic acid supplements and SSRI medication by pregnant women on language development in their offspring at age 3 years.

Methods: Design: Cohort study.

Setting: 45 266 women with 51 747 singleton pregnancies in the population-based Norwegian Mother and Child Cohort study (1999–2008).

Exposure: Validated self-reported use of folic acid supplements and SSRIs was prospectively collected in subsequent 4 weeks intervals during pregnancy.

Main outcome measures: Children's language competence was measured by a validated language grammar rating scale.

Statistical analysis: The association between different combinations of folic acid and SSRI use and language competence in the offspring was investigated using multinomial logistic regression (three outcome categories)

Results: Women reported use of folic acid in 44 417 (85.8%) and SSRI in 372 (0.7%) of the pregnancies; 260 used the two simultaneously. The relative risk ratio (RRR) of lower language competence increased with increasing duration of simultaneous use of folic acid and SSRIs, reaching adjusted RRR = 4.5 (95%CI, 2.5–8.0) and 5.7 (2.5–13.0) for the middle and the most delayed category, respectively, after simultaneous use in 4–8 intervals compared with mothers who used folic acid as recommended and no SSRIs and using the best language competence category as the reference. Using SSRIs, but not simultaneously with folic acid, gave no increased risk.

Conclusions: A significant association between long-term simultaneous use of folic acid and SSRIs during pregnancy and delayed language competence was detected in the offspring. This surprising result may have a biological explanation but warrants further studies.

454. Selective Serotonin Reuptake Inhibitor Use in First Trimester Pregnancy and Risk of Congenital Anomalies: A EUROmediCAT Case-malformed Control Study in 12 Countries

B Boyle,[1] M Loane,[1] M Bakker,[2] MC Addor,[3] L Arriola,[4] E Garne,[5] M Gatt,[6] S Jordan,[7] B Khoshnood,[8] K Klungsoyr,[9] V Nelen,[10] A Neville,[11] M O'Mahoney,[12] A Pierini,[13] A Rissman,[14] D Tucker,[15] A Wiesel,[16] H Dolk.[1] *[1]WHO Collaborating Centre for Surveillance of Congenital Anomalies, Ulster University, Newtownabbey, Northern Ireland, UK; [2]University Medical Centre Groningen, Groningen, The Netherlands; [3]Division of Medical Genetics, CHUV, Lausanne, Switzerland; [4]Registro Anomalias Congenitas, Subdireccion de Salud Publica, San Sebastian, Spain; [5]Hospital Lillebaelt, Kolding, Denmark; [6]Directorate for Health Information and Research, Guardamangia, Martinique; [7]Dept Nursing, Swansea University, Swansea, UK; [8]Paris Registry of Congenital Malformations, INSERM UMR1153, Paris, France; [9]Dept Global Public Health and Primary Care, University of Bergen and Norwegian Institute of Public Health, Bergen, Norway; [10]Provincial Institute for Hygiene, Antwerp, Belgium; [11]Emilia Romagna Registry of Birth Defects, Universitaria di Ferrara, Ferrara, Italy; [12]Health Service Executive, Cork, Ireland; [13]CNR-Institute of Clinical Physiology, National Research Council, Pisa, Italy; [14]Malformation Monitoring Centre, Medical Faculty Otto-von-Guericke University, Magdeburg, Germany; [15]CARIS, Public Health Wales, Swansea, UK; [16]Dept Paediatrics, University Medical*

Centre of the Johannes Gutenberg University, Mainz, Germany.

Background: There is evidence that selective serotonin reuptake inhibitor (SSRI) antidepressants used in early pregnancy may cause congenital anomalies (CA), particularly congenital heart defects (CHD).

Objectives: The aim of this study was to determine the association between first trimester pregnancy exposure to SSRI and specific CAs, using EUROCAT registry data enhanced with linkage to prescription databases.

Methods: Population-based case-malformed control study covering 3.3 million births from 14 EUROCAT registries in 12 countries, 1995–2012. CAs included non-syndromic livebirths, fetal deaths and terminations of pregnancy for fetal anomaly ($n = 71\,602$ babies). Exposure to SSRI among cases of CHD ($n = 24\,035$) and 15 non-CHD CA signals ($n = 25\,752$) derived from the literature was compared with controls (babies with non-CHD, non-signal CA only, $n = 21\,815$). Medication exposure information was obtained from prospective medical records (13 registries), maternal interviews after delivery (two registries) and prescription records (five registries). Odds ratios (OR, 95%CI) were adjusted for registry and time.

Results: SSRI exposure was associated with a low and non-significant risk of CHD overall (OR 1.12, 95%CI 0.90–1.37) and severe CHD (OR 1.27, 95%CI 0.94–1.71) relative to control CA; specific associations for severe CHD with citalopram (OR 1.76, 95%CI 1.05–2.95) and SSRI with Ebstein's anomaly (OR 4.24, 95%CI 1.69–10.6) were found. Elevated risks were found for four non-CHD signals: gastroschisis (OR 2.15, 95%CI 1.27–3.64), renal dyplasia (OR1.97, 95%CI 1.26–3.07), clubfoot (OR 1.56, 95%CI 1.12–2.17) and anorectal atresia (OR 1.79, 95%CI 0.96–3.32).

Conclusions: The excess risk of CHD associated with SSRI use overall is small. The specific associations regarding citalopram and Ebstein's anomaly need confirmation in independent datasets. Evidence is accumulating that some other types of CA may also be associated with SSRI use. Further research is needed to explore the causality of these associations, particularly with regard to underlying condition and co-exposures.

455. 5-Year Experience with the Cymbalta Pregnancy Registry: A Prospective Observational Study to Assess Duloxetine Exposure during Pregnancy

Hu Li, Mark Bangs, Jennifer Zimmer, Dawn Dyer, Sheila Miller. *Eli Lilly, Indianapolis, IN, USA.*

Background: Cymbalta (duloxetine HCl) is a serotonin-norepinephrine reuptake inhibitor approved in the USA. Many of the approved indications are prevalent in women of childbearing age. A pregnancy registry was established in July 2009.

Objectives: The primary objective is to estimate the risk of major congenital anomalies among pregnancies exposed to duloxetine in the USA.

Methods: This is a US-based, voluntary, observational, exposure-registration, and follow-up study of women taking duloxetine during pregnancy. Data are collected at registration, the end of the second trimester, the outcome of pregnancy, and 4 and 12 months of infant age. Breastfeeding mothers completed a questionnaire at 3, 6, 9, and 12 months postpartum. The registry is overseen by an independent Advisory Committee and managed by INC Research on behalf of Eli Lilly and Company. The enrollment target is 484 pregnancies before the outcome of pregnancy is known.

Results: From July 2009 to August 2014, 74 prospective cases were enrolled (58 with a known pregnancy outcome, 9 with pending pregnancy outcomes, and 7 lost to follow-up). Reported outcomes include 56 live births, 2 spontaneous abortions, and 0 stillbirths, induced abortions, ectopic pregnancies, molar pregnancies, or maternal deaths resulting in fetal death. Six premature births and three birth defects were reported. Follow-up was completed at outcome for 48 infants, at 4-month assessment for 44 and at 12-month assessment for 33. Pediatric outcomes include four infants with abnormal development for their age and one poor neonatal adaptation. Birth defect rates were not calculated because of the small number of reported cases.

Conclusions: The registry study supplements the ongoing monitoring of the safety of duloxetine in pregnancy. The inability to calculate accurate rates of birth defects due to the slow enrollment and small number of cases reported to the registry thus far

limits any reliable and definitive conclusions regarding the safety of duloxetine in pregnancy. Information regarding the Registry may be obtained by calling 1-866-814-6975 or by visiting www.cymbaltapregnancyregistry.com.

456. Antipsychotics in Pregnancy: Comparative Cohort Studies of Women Treated Before and During Pregnancy

Irene Petersen,[1] Rachel L McCrea,[1] Cormac J Sammon,[1] Stephen JW Evans,[2] David Osborn,[3] Phil J Cowen,[4] Irwin Nazareth.[1] *[1]Primary Care and Population Health, UCL, London, UK; [2]Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; [3]Division of Psychiatry, UCL, London, UK; [4]Department of Psychiatry, Oxford University, Oxford, UK.*

Background: Antipsychotic medication is commonly prescribed to women with schizophrenia and increasingly to women with bipolar disorders. Many face a dilemma when they become pregnant or plan pregnancy as to whether to continue the antipsychotic medication. Yet, very limited information is available on the safety in pregnancy.

Objectives: The aim of this study was to examine the characteristics and risks of adverse birth outcomes between women who continue to receive antipsychotic treatment versus those who discontinue in pregnancy and those without antipsychotic treatment.

Methods: Using data from The Health Improvement Network (THIN) primary care UK database, we did a comparative cohort study of women receiving antipsychotic prescriptions (1) before pregnancy, but not in pregnancy ($N=141$), (2) before and during 1st trimester of pregnancy ($N=175$) and (3) without antipsychotic treatment before and during pregnancy ($N=211\,719$).

Results: The characteristics of women in the three cohorts varied. Women who discontinued antipsychotics in pregnancy were younger (median age: 29 (IQR: 25–34)) than women who continued treatment in the first trimester (33 (28–37)) and women not on antipsychotics (31 (26–34)). A relatively large proportion of the women on antipsychotic treatment before or during pregnancy had a history of drug use (13% and 14%) or alcohol problems (5% and 8%) in contrast to less than 1% of women not on treatment. A larger proportion of the women on antipsychotic treatment before or in pregnancy were also obese (11% and 21%) and smokers (36% and 46%) than women not on treatment (6% and 20%). The proportion of children born with major congenital malformations among those who continued antipsychotic treatment in the first trimester was similar to that among women who discontinued before the first trimester (RR 1.2 CI95 0.2–7.2) and women without treatment (RR 0.8 CI95 0.3–2.6).

Conclusions: Women who receive antipsychotic treatment before and during pregnancy differed on several characteristics from women not receiving treatment. However, we did not find a substantial difference in the proportion of children born with major congenital malformations between the three groups.

457. Use of Topiramate in Relation to the Risk of Orofacial Clefts

Hao Wang,[1] Maria Loane,[2] Joan Morris,[3] Ester Garne,[4] Vera Nelen,[5] Babak Khoshnood,[6] Anke Rißmann,[7] Awi Wiesel,[8] Mary O'Mahony,[9] Anna Pierini,[10] Amanda Neville,[11] Miriam Gatt,[12] Hermien de Walle,[13] Marie-Claude Addor,[14] David Tucker,[15] Kari Klungsoyr,[16] Anna Latos-Bielenska,[17] Jan Mejnartowicz,[18] Christine Verellen-Dumoulin,[19] Bérénice Doray,[20] Larraitz Arriola,[21] Ingeborg Barisic,[22] Elisa Calzolari,[11] Diana Wellesley,[23] Helen Dolk,[2] Lolkje de Jong-van den Berg.[1] *[1]University of Groningen, Groningen, The Netherlands; [2]University of Ulster, Ulster, UK; [3]Queen Mary University of London, London, UK; [4]Lillebaelt Hospital, Kolding, Denmark; [5]Provinciaal Instituut voor Hygiene, Antwerp, Belgium; [6]Institut National de la Sante et de la Recherche Medicale, Paris, France;[7]Otto-von-Guericke Universitaet Magdeburg, Magdeburg, Germany; [8]Johannes Gutenberg Universitat, Mainz, Germany; [9]St Finbarr's Hospital, Cork, Ireland; [10]Istituto di Fisiologia Clinica del Consiglio Nazionale delle Ricerche, Pisa, Italy; [11]Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy; [12]Department of Health Information and Research, Malta; [13]University Medical Centre Groningen, Groningen, The Netherlands; [14]Registre Vaudois des Malformations, Lausanne, Switzerland; [15]Public Health Wales NHS Trust, Wales, UK; [16]Medical Birth Registry of Norway, Bergen, Norway; [17]Polish Registry of Congenital Malformations, Poznan, Poland; [18]Uniwersytet Medyczny im. Karola Marcinkowskiego*

w Poznaniu, Poznan, Poland; [19]Institut de Pathologie et de Génétique, Charleroi, Belgium; [20]Registre des Malformations Congenitales D'Alsace, France; [21]Registro Anomalias Congénitas CAPV, Vitoria-Gasteiz, Spain; [22]Children's University Hospital Zagreb, Zagreb, Croatia; [23]Princess Anne Hospital, UK.

Background: The use of topiramate (TPM) has been increased among pregnant women. Safety data for TPM in human pregnancy are limited. Recent studies have suggested that exposure to TPM early in gestation has a higher risk of orofacial clefts (OCs), particularly cleft lip with or without palate, and there has been a Food Drug Administration (FDA) alert.

Objectives: The aim of this study was to assess the risk of OCs relative to other malformations in infants whose mothers had taken TPM during the first trimester of pregnancy.

Methods: A population-based case–control study with malformed controls was performed using the EUROCAT Antiepileptic (AED) Drug Database including data from 19 population-based registries of congenital anomaly in Europe with a total coverage of 8.0 million births from 1995 to 2011. Cases were 10 802 nonsyndromic OC registrations, of whom 8919 were isolated, and 6827 were cleft lip with or without cleft palate (CL/P). Controls were 136 838 nonchromosomal, non-OC registrations. We compared first trimester TPM use versus no-AED use, for monotherapy and polytherapy.

Results: Exposure to TPM monotherapy was recorded for a total of 12 registrations, with one registration in the case group (isolated cleft palate) and 11 in the control group (odds ratio (OR) 1.15, 95% CI 0.03–7.95 for OC relative to other malformations, OR 4.03, 95%CI 0.09–27.8 for isolated cleft palate). No registration of CL/P was in TPM monotherapy exposure. There were 36 registrations exposed to TPM polytherapy, of whom six with isolated CL/P, three with cleft palate. Out of 36 of TPM polytherapy, 19 included valproic acid, 8 included carbamazepine and 4 included lamotrigine. The OR for TPM polytherapy versus no-AED use was 4.23 (95%CI 1.75–9.28) for OC, 4.35 (95%CI 1.31–11.5) for isolated CL/P and 3.85 (95%CI 0.75–12.5) for isolated cleft palate.

Conclusions: The prevalence of TPM monotherapy exposure was five times lower in these data than reported in the United States, which limited our ability to confirm or refute previous findings. We found an excess of OCs, particularly CL/P, associated with TPM polytherapy. Further attention to TPM polytherapy is warranted.

458. Prenatal Triptan Exposure and Psychomotor Changes in 18- and 36-month-old Norwegian Children

Mollie Wood,[1] Kate Lapane,[1] Jean Frazier,[2] Nordeng Hedvig.[3] *[1]Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA; [2]Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA; [3]School of Pharmacy, University of Oslo, Oslo, Norway.*

Background: Triptans are migraine medications with affinity for serotonin 1B/D receptors, which are active in fetal brain development. Studies of triptan exposure on psychomotor outcomes beyond the post-partum period are scant.

Objectives: The aim of this study was to examine risk of psychomotor problems associated with prenatal triptan exposure and whether this risk changes between 18 and 36 months of age.

Methods: The Norwegian Mother and Child Cohort Study is a longitudinal study that linked birth registry data to questionnaires regarding exposures during the perinatal period. We identified 101 625 live singleton births without major malformations who were present at either 18 and 36 month postpartum follow-up ($n = 51\,855$). Generalized estimating equations provided estimates of change in odds of developmental problems over time for each group (z score ≥ 1.5), measured by the Ages and Stages Questionnaire (fine and gross motor and communications subscales), reported as the adjusted change in odds (aOR) with 95% confidence intervals (CI).

Results: One percent ($n = 500$) used triptans during pregnancy (TDP), 2% used triptans prior to pregnancy only (TPP), 8% had migraines without triptan use (M), and 89% had no history of migraine/triptan use (NMT). The rate of psychomotor problems tended to decrease over time for all groups, for communication (aOR 0.44, 95%CI 0.42 to 0.47), fine motor (aOR 0.79; 95%CI 0.76 to 0.83), and gross motor problems (aOR 0.36; 95%CI 0.34 to 0.39). TDP had reduced odds of gross motor problems at

36 but not 18 months, with a 55% decrease in odds of gross motor problems between 18 and 36 months compared with the TPP (aOR 0.45; 95%CI 0.19 to 0.46), a 65% decrease relative to M (aOR 0.35, 95%CI 0.28 to 0.44), and a 63% decrease compared with NMT (aOR 0.37; 95%CI 0.15 to 0.91). We observed no differences between groups at 18 or 36 months for communication or fine motor problems.

Conclusions: Children with prenatal triptan exposure were less likely to have gross motor problems at 36 months relative to all comparison groups; no association was observed for fine motor or communication problems. Exploration of the timing of exposure using marginal structural models may help explain these findings.

459. Is Exposure to Benzodiazepine during Pregnancy Increase the Risk of Spontaneous Abortion?

Odile Sheehy,[1] Anick Bérard.[1,2] *[1]Research Center, CHU Sainte-Justine, Montreal, QC, Canada; [2]Faculty of pharmacy, University of Montreal, Montreal, QC, Canada.*

Background: Benzodiazepines (BZDs) are frequently prescribed during pregnancy. It is recognized that BZDs cross the placental barrier and may represent a hazard for the fetus. To our knowledge, no study has looked at the risk of spontaneous abortion (SA) associated with gestational BZDs exposure.

Objectives: The aim of this study was to estimate the risk of SA associated with BZDs use as a class, and for each BZDs types separately, during early pregnancy.

Methods: We conducted a nested case–control study in the Quebec Pregnancy Cohort, between January 1998 and December 2008. After excluding pregnancies exposed to fetotoxic drugs, or a diagnosis of epilepsy, 17 367 cases of SA were identified. Index date was the gestational age of SA diagnosis. Cases were randomly matched to five controls on the index date and calendar year of pregnancy. Use of BZDs was defined by filled prescriptions between the 1st day of gestation until the index date and was compared with nonuse during the same time window. We also studied each specific type of BZDs separately (alprazolam, bromazepam, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, oxazepam, temazepam, and triazolam). Conditional generalized estimation equation (GEE) regressions were used to estimate crude and adjusted odds ratios (OR), and 95% confidence intervals (95%CI), taking into account the indication and the use of other medications.

Results: A total of 703 (4.1%) of the 17 367 pregnancies ending with an SA had at least one filled prescription of BZDs during early pregnancy, as compared with 1553 (1.8%) of the matched controls (OR 2.24, 95%CI 2.05–2.45). Adjusting for potential confounders, we found that use of BZDs during early pregnancy was associated with an increased risk of SA (OR 1.72, 95%CI 1.54–1.92). We also observed an increased risk of SA for each type of BZDs, but the difference reaches statistical significance for alprazolam, bromazepam, clonazepam, lorazepam, and temazepam.

Conclusions: Maternal exposure to BZDs, overall, and specifically for alprazolam, bromazepam, clonazepam, lorazepam, and temazepam during pregnancy was associated with an increased risk of SA, taking into account the indication and the use of other medications.

460. Prenatal Acetaminophen Exposure and Cortical Thickness in Typically Developing Children

Mollie Wood,[1] David Kennedy,[2] Steven Hodge,[2] Jean Frazier.[2] *[1]Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA; [2]Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA.*

Background: Studies have shown an increased risk of attention-deficit/hyperactivity disorder (ADHD) or ADHD-like symptoms in children with prenatal acetaminophen (ACET) exposure. No studies to date have examined differences in cortical thickness associated with ACET exposure.

Objectives: The aim of this study was to compare cortical thickness in children with and without prenatal ACET exposure.

Methods: The PING study is a cross-sectional multisite study of neurotypical youth. This analysis studied 782 children aged 3 to 20 years, for whom a maternal report of pregnancy exposures was available.

Pregnancy exposure to ACET was determined by maternal report. Neuroanatomy was measured using FreeSurfer on MP-RAGE scans acquired for each participant. We conducted a propensity score matched analysis in which each exposed individual was matched to seven unexposed controls using greedy matching without replacement. We conducted a multivariate analysis of variance in the matched sample. Results are reported as the overall association between ACET exposure and all 32 cortical regions studied, as well as the linear association between exposure and each cortical region (β) with 95% confidence intervals (CI).

Results: Propensity matching retained 27 of 38 ACET exposed children and 208 of 744 unexposed comparators. We found evidence of a global association between ACET and cortical thickness ($F = 1.47$, $p = 0.06$). Multiple cortical regions were associated with ACET: cuneus (β 0.09, 95%CI 0.02 to 0.17), inferior temporal (β 0.08, 95%CI 0.01 to 0.14), lateral occipital (β 0.06, 95%CI 0.00 to 0.12), lateral orbitofrontal (β 0.11, 95%CI 0.03 to 0.18), lingual (β 0.09, 95%CI 0.02 to 0.15), parahippocampal (β 0.21, 95%CI 0.10 to 0.32), pericalcarine fissure (β 0.08, 95%CI 0.02 to 0.14), postcentral (β 0.06, 95%CI 0.00 to 0.11), rostral middle frontal cortex (β 0.08, 95%CI 0.02 to 0.15), superior frontal (β 0.07, 95%CI 0.01 to 0.13), superior temporal (β 0.07, 95%CI 0.00 to 0.13), supramarginal (β 0.07, 95%CI 0.01 to 0.13), frontal pole (β 0.14, 95%CI 0.01 to 0.28), and transverse temporal (β 0.12, 95%CI 0.02 to 0.22).

Conclusions: This translational study links prenatal acetaminophen exposure to cortical thickness in multiple brain regions.

461. Exposure to Prescription Opioid Analgesics In-Utero and the Risk of Neonatal Abstinence Syndrome: A Population-based Cohort Study

Rishi J Desai,[1] Krista F Huybrechts,[1] Sonia Hernandez-Diaz,[2] Elisabetta Patorno,[1] Brian T Bateman.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA; [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: The use of prescription opioids for treating pain in pregnancy is common and increasing. The risk of neonatal abstinence syndrome (NAS) associated with prescription opioids is not well understood.

Objectives: The aim of this study was to describe the risk of neonatal abstinence syndrome (NAS) in infants born to women using prescription opioids in the presence or absence of additional NAS risk factors, including history of opioid abuse or dependence, abuse of other substances, non-opioid psychotropic drug use, and smoking.

Methods: Data were derived from the Medicaid Analytic Extract (MAX) from 46 US states. We defined a cohort of women who filled ≥1 outpatient prescription for an opioid at any time during pregnancy. Exposure characteristics including duration of therapy (short-term (<30 days) or long-term (≥30 days)), timing of use (early use (only in the first two trimesters) or late use (extending into the third trimester)), and cumulative dose (in morphine-equivalent milligram) were assessed. The primary outcome was a diagnosis of NAS among the live-born infants.

Results: A total of 1705 cases of NAS were identified among the infants of 290 605 pregnant women filling opioid prescriptions. Long-term opioid use during pregnancy resulted in higher risk of NAS (reported per 1000 deliveries (95% confidence interval)) in the presence of additional risk factors of known opioid abuse (220.2 (200.8 to 241.0)), alcohol or other drug abuse (30.8 (26.1 to 36.0)), exposure to other psychotropic medications (13.1 (10.6 to 16.1)), and smoking (6.6 (4.3 to 9.6)) than in the absence of any of these risk factors (4.2 (3.3 to 5.4)). The corresponding risk estimates for short-term use were 192.0 (175.8 to 209.3), 7.0 (6.0 to 8.2), 2.0 (1.5 to 2.6), 1.5 (1.0 to 2.0), and 0.7 (0.6 to 0.8) per 1000 deliveries, respectively. Late use of prescription opioids in pregnancy generally resulted in higher NAS risk compared with early use.

Conclusions: This large population-based cohort study indicates that short-term use of prescription opioids for treating acute pain during pregnancy is associated with a very low risk of deliveries with NAS in the absence of additional risk factors.

462. SNRI, Bupropion and Mirtazapine Use During Pregnancy and the Risk of PPHN

Anick Bérard, Odile Sheehy, Sasha Bernatsky, Michal Abrahamowitz. *CHU Ste-Justine, Montreal, Canada;*

University of Montreal, Montreal, Canada; McGill University, Montreal, Canada.

Background: Studies from the USA and Scandinavia have shown that SSRI use during pregnancy, specifically after the 20th week of gestation, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). As of now, however, limited data are available on the risk of PPHN associated with other types of antidepressants such as SNRI (venlafaxine, desvenlafaxine, and duloxetine), bupropion, and mirtazapine.

Objectives: The aim of this study was to quantify the association between SNRI, bupropion, and mirtazapine use during pregnancy and the risk of PPHN.

Methods: This study was performed in the Quebec Pregnancy Cohort between 1998 and 2009. To be eligible, women had to be covered by their provincial drug plan at least 12 months before and during pregnancy and have a live birth. Pregnancies resulting in stillbirths or neonatal deaths with a known cause of death were also eligible. Confounding by indication was minimized by adjusting for history of maternal depression before and during pregnancy. Exposure categories were SNRI, bupropion and mirtazapine use, and other antidepressant use. The time-window of interest was the second half of pregnancy (21 gestational week until the end of pregnancy). Index date was the time of delivery. PPHN was identified in the first year of life. Case–control analyses were performed using GEE models, taking into account potential confounders including the indication.

Results: Overall, 76 405 pregnancies met inclusion criteria and were considered; PPHN was identified in 0.2% of newborns. During the second half of pregnancy, 0.29% SNRI, 0.02% bupropion, and 0.01% mirtazapine were identified. Adjusting for maternal depression, and other confounders, SNRI use during the second half of pregnancy was not statistically significantly increasing the risk of PPHN (OR 1.85, 95%CI 0.56, 6.14) compared with non-use. Although mirtazapine and bupropion use during the second half of pregnancy compared with non-use did not seem to increase the risk of PPHN, the small number of exposed cases did not enable multivariate analyses.

Conclusions: This study did not show a statistically significant increased risk of PPHN with second/third trimester exposure to SNRI, mirtazapine, or bupropion.

463. Detection Bias in the Prenatal Diagnosis of Malformations among SSRI-exposed Women

Anna M Modest,[1] Marth M Werler,[1,2] Carla Van Bennekom,[2] Allen A Mitchell.[1,2] *[1]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; [2]Slone Epidemiology Center, Boston University, Boston, MA, USA.*

Background: Selective serotonin reuptake inhibitors (SSRIs) in pregnancy have been inconsistently associated with birth defects, particularly cardiac defects. If exposure to SSRIs prompted efforts to identify defects through rigorous prenatal ultrasound (US) screening, detection bias may account for positive associations.

Objectives: The aim of this study was to determine whether SSRI exposure in pregnancy is associated with higher proportions of structural defects being identified by US.

Methods: For 1998–2014, we studied all mothers of babies with malformations from the Slone Birth Defects Study, a case–control study of malformed and non-malformed infants in North America. Women were interviewed within 6 months after delivery about medication use, illnesses, and prenatal care. Those who received fertility treatment and had seizures, diabetes, multiple births, or unknown SSRI exposure status were excluded. Because information on negative ultrasounds was not available, we compared, among SSRI-exposed and unexposed pregnancies, the proportions of structural malformations that were identified by USA. Log-binomial regression was used to estimate the RR and 95%CI.

Results: Among 15 632 mothers of malformed infants, 680 (4.4%) were exposed to an SSRI. For all defects, after adjustment for maternal age, race, center of birth, and year of baby's birth, prenatal diagnosis was not associated with SSRI exposure (aRR 1.0, 95%CI 0.95–1.1). When defects were grouped according to organ system, no associations were observed. Of particular interest, the aRR for cardiac defects was 1.0 (0.91–1.1).

Conclusions: We saw no evidence that US-detected defects were more common among SSRI-exposed babies, suggesting that detection bias resulting from SSRI exposure was unlikely to explain observed associations.

464. Neonatal Drug Withdrawal Syndrome: Cross-country Comparison of Recorded Hospital Admissions in England, USA, Western Australia and Ontario, Canada

Hilary R Davies, Ruth Gilbert, Irene Petersen, Irwin Nazareth, Arturo Gonzalez-Izquierdo. *Primary Care and Population Health, UCL, London, UK.*

Background: Misuse of addictive drugs, particularly opiates, during pregnancy is a multifaceted public health problem.

Objectives: We determined trends over time in the birth prevalence of neonatal drug withdrawal syndrome (NWS) in England compared with reported trends for USA, Western Australia and Ontario, Canada and variation in birth prevalence in the English NHS by hospital trusts, maternal age and birth weight.

Methods: We conducted a retrospective cohort study using national hospital administrative data for babies admitted to NHS hospitals in England in 1997–2011. Published annual prevalence rates for other countries were confirmed with authors. Annual prevalence of NWS per 1000 live births based on ICD diagnostic codes in hospital admission data was as follows: for English NHS in 2011, the proportion of English NHS hospital trusts outside 3 standard deviations (sd) of mean prevalence and unadjusted odds ratios for associations between maternal age and birth weight with NWS.

Results: Mean prevalence rates increased in all four countries but stabilised in England and W. Australia and continued to rise in the USA and Ontario. Most recent birth prevalence is 2.73/1000 live births in England (2011; 1544 cases), 3.5 /1000 in W. Australia (2005), 3.6/1000 in the USA (2009) and 5.1/1000 in Ontario (2011). In England in 2011, unadjusted birth prevalence was outside 3 sd of the mean in 22% of hospital trusts (12% above, 10% below). Risk of NWS was marginally increased for mothers aged 30–34 years (unadjusted odds 24.6% of NWS) and for babies weighing 1500–2500 g at birth (unadjusted OR 3.49, 95%CI 3.05–3.98, 19% of NWS).

Conclusions: Although NWS is stable in England, rising rates in the USA and Ontario highlight the need for national NWS surveillance and for investigation of the wide variation in recording between NHS trusts. Linkages between administrative data for mother and baby, and including health and social care provision, offer an efficient resource for policy makers to monitor who is affected and how management and outcomes vary for mothers and babies.

465. The Impact of Different Case Ascertainment Definitions on the Prevalence of Major Congenital Malformations and Their Association with Asthma During Pregnancy

Sherif Eltonsy,[1,2] Amelie Forget,[1,2] Lucie Blais.[1,2] *[1]Faculty of Pharmacy, Universite de Montreal, Montreal, QC, Canada; [2]Hopital du Sacré-Cœur de Montréal, Montreal, QC, Canada.*

Background: Accurate identification of major congenital malformations cases (MCM) from administrative databases is crucial for perinatal epidemiology. In Quebec, most of MCM are detected in hospital; however, medical claims database captures diagnoses from both hospitals and ambulatory medical facilities.

Objectives: The objectives of this study were to compare the prevalence of MCM using different case definitions that vary by the source of data and the classification method and to evaluate the impact of those definitions on the maternal asthma MCM association.

Methods: We used the Quebec Asthma and Pregnancy Database to form a cohort of pregnancies from women with and without asthma who delivered between 1990 and 2010. Two methods for MCM classification were used: (1) two-step congenital malformation classification (TCMC) and (2) Canadian Congenital Anomalies Surveillance System (CCASS). Three case definitions were compared within each classification method: (1) ≥1 MCM diagnosis in the hospital database, (2) ≥1 MCM diagnosis in the hospital database or ≥2 MCM diagnoses in the medical claims database, and (3) ≥1 MCM diagnosis in the hospital database or ≥1 MCM diagnosis in the medical claims database. We calculated the prevalence of MCM identified in the first year of life using the six case definitions. Crude and adjusted odds ratios (ORs) of MCM associated with maternal asthma were calculated using generalized estimating equations models.

Results: From 467 946 pregnancies, 12.3% were from women with asthma. MCM prevalence ranged between 5.1% and 7.1% with the TCMC and 7.0% and 10.6% with the CCASS. The prevalence of MCM increased when medical claims data were added to hospital data. Asthma was significantly associated with MCM with slightly weaker estimates with CCASS than TCMC

(aOR 1.14 to 1.20 vs 1.22 to 1.26). The TCMC gave reliable results with all correlation structures tested.

Conclusions: The case definition had a considerable impact on the prevalence of MCM but much less impact on aORs. The TCMC method provided more stable OR estimates.

466. Asthma Medication During Pregnancy: A Cohort Study in EFEMERIS Database

Anna-belle Beau,[1] Alain Didier,[2] Isabelle Lacroix,[1] Caroline Delarue-Hurault,[1] Jean-Louis Montastruc,[1] Christine Damase-Michel.[1] *[1]Service de Pharmacologie Médicale et Clinique, Faculté de Médecine, Université Toulouse III, CHU, INSERM1027, Toulouse, France; [2]Service de Pneumologie, Hôpital Larrey, Centre Hospitalier Universitaire, Toulouse, France.*

Background: Asthma affects around 8% of pregnant women. Studies show that women experience changes in prescriptions for asthma medications during pregnancy, maybe because of concerns about their potential adverse effects on the fetus.

Objectives: The aim of this study was to describe asthma medications before and during pregnancy in France.

Methods: Women from EFEMERIS, a French database including prescribed and dispensed reimbursed drugs during pregnancy and pregnancy outcomes, who delivered between 1 July 2005 and 31 December 2012 were included. Women with at least two dispensations for any asthma medication (ATC code R03) from the 30 days prior to conception through their date of delivery were considered to be asthmatic.

Results: 2977 women over 69 205 (4%) were identified as asthmatic. Almost 62% of asthmatic women received at least one prescription of short-acting β2-agonist (SABA); 63%, at least one inhaled corticosteroid (IC); 42%, a fixed combination of IC and long-acting β2-agonist (LABA); and 8%, a LABA. Both increased use of SABA and IC and decreased use of fixed combination were observed through pregnancy compared with pre-pregnancy period. Women received 3.5 ± 2.7 asthma medications during the period. Asthmatic women were older, had more long-term adverse health conditions, were more frequently smokers and suffered more from diabetes compared with non-asthmatic women ($p < 0.05$). The characteristics of children in terms of pregnancy duration, birth weight, neonatal pathology and congenital anomaly were not different between asthmatic and non-asthmatic women ($p > 0.05$).

Conclusions: Exposition to antiasthmatic drugs varies during pregnancy, with short-acting β2-agonist and inhaled corticosteroid being the more prescribed. Our study shows no difference concerning child health between asthmatic and non-asthmatic women.

467. The Use of Antiasthmatic Medications During Pregnancy and the Risk of Gestational Diabetes

Veronique Baribeau,[1] Marie-France Beauchesne,[1,3] Evelyne Rey,[4] Amelie Forget,[2] Lucie Blais.[1,2] *[1]Universite de Montreal, Montreal, Canada; [2]Hopital du Sacre-Coeur de Montreal, Montreal, Canada; [3]Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Canada; [4]Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada.*

Background: Asthma is one of the most common chronic conditions in pregnancy. Very few studies have examined the risk of gestational diabetes in association with the use of antiasthmatic medications during pregnancy, although preliminary data suggest an increased risk.

Objectives: The aim of this study was to evaluate whether the risk of gestational diabetes increases with the dose of inhaled corticosteroids (ICS) and the use of long-acting beta2-agonists (LABA) among pregnant asthmatic women.

Methods: We used a case–control design nested within a cohort of 12 587 pregnancies from asthmatic women who delivered between 1998 and 2010 reconstructed from the linkage of Québec's administrative databases. Gestational diabetes was defined by at least one diagnosis of gestational or chronic diabetes recorded or a prescription for an antidiabetic medication filled after the 20th week of gestation. Each case of gestational diabetes was matched to 10 controls according to calendar year and gestational age at the time of the outcome. The use of asthma medications was measured at the time of the outcome for cases or selection for controls. ICS were categorized as no use (reference), low dose (<250 ug, fluticasone-equivalent), medium dose (250–499 ug) and high dose (≥500 ug). LABA was considered as a dichotomous variable (use vs. no use). Conditional logistic regression was used to estimate odds ratio adjusted for risk factors of gestational diabetes, including asthma severity and control. The impact of

ICS was estimated among women unexposed to LABA, while the impact of LABA was estimated among women exposed to ICS.

Results: One thousand cases of gestational diabetes were identified from the cohort. Higher risks of gestational diabetes were observed for higher doses of ICS (low dose OR = 0.96; 95%CI: 0.75–1.23; medium dose OR = 1.37; 95%CI: 0.93–2.02; and high dose OR = 1.46; 95%CI: 0.86–2.47) and for the use of LABA (OR = 1.24; 95%CI: 0.67–2.3). However, none of these associations were statistically significant.

Conclusions: There is a trend for a dose–response relationship between ICS and gestational diabetes and for an increased risk with LABA use. More studies need to be carried out to conclude about these associations.

468. Association between Folic Acid Supplementation and Neural Tube Defects among High-risk Pregnancies

Corey M Benedum,[1] Samantha E Parker,[2] Allen A Mitchell,[1] Martha M Werler.[1,2] *[1]Slone Epidemiology Center at Boston University, Boston, MA, USA; [2]Epidemiology, Boston University School of Public Health, Boston, MA, USA.*

Background: Neural tube defects (NTDs) occur within 28 days of conception when the neural tube fails to properly close. Daily folic acid (FA) intake of 0.4 and 4 mg is recommended to prevent the occurrence and recurrence of NTDs, respectively. However, the effectiveness of daily 0.4 mg of FA among high-risk pregnancies is unclear.

Objectives: The aim of this study was to examine the relationship between FA supplementation and dose and the risk of NTDs among pregnancies at high-risk for NTDs.

Methods: The Slone Epidemiology Center Birth Defects Study was used to identify 229 cases of NTDs (1988–2012) and 1573 controls with either minor anomalies (1988–1993) and no major malformations (1993–2012). Mothers were interviewed within 6 months after delivery. "High risk" included women with a first-degree or second-degree family history of CNS malformations ($n = 336$), antiepileptic drug (AED) use ($n = 138$), pre-pregnancy obesity ($n = 1258$), or pre-existing diabetes ($n = 72$). We evaluated any daily FA supplementation and, when numbers permitted, average daily FA intake doses (mg) (0, 0.01–0.399, 0.4, 0.401–0.99, 1, 1.01–3.99, and ≥4 mg) for the 28 days before and after the last menstrual period. Poisson regression models adjusting for study center were used to estimate risk ratios (RRs) and 95% confidence intervals (CIs).

Results: A reduced risk of NTDs was associated with FA supplementation among women using AEDs (RR: 0.8; CI: 0.3–2.2) and women with pre-existing diabetes (0.5; 0.1–3.9). Among those with pre-pregnancy obesity, FA supplementation was not associated with NTDs (1.03; 1.0–1.1). Among women with a positive family history, NTD risk was reduced for any FA supplementation (0.4; 0.2–0.7) and across dose levels (e.g., <0.4 mg: 0.8; 1.01–3.99 mg: 0.4). Of those with a family history, 1.5% of controls had daily intakes of ≥4 mg, but there were no cases (~1 case expected).

Conclusions: Our results suggest that FA supplementation at the recommended levels might reduce the risk of an NTD-affected pregnancy among women taking AEDs in pregnancy and those with pre-existing diabetes. Our findings are also compatible with the recommendation for higher doses of FA among women with a family history of CNS malformations.

469. Factors Associated with Achieving Success for Pregnancy Registries

Deborah Covington, Kristin Veley, Ann Mallard. *Registries & Observational Studies, PPD, Wilmington, NC, USA; Global Late Stage Research, PPD, Morrisville, NC, USA; Clinical Management, PPD, Wilmington, NC, USA.*

Background: FDA's exploratory review of pregnancy registries defined four measures of registry success: achievement of target enrollment, reference of registry data in clinical guideline(s), change in a product's label due to registry findings, and publication of registry results in peer-reviewed journal(s). FDA acknowledged limitations of its review, including failure to assess other factors that may contribute to registry success such as product usage and registry awareness.

Objectives: The aim of this study was to build upon FDA's evaluation by examining the association between other factors and registry success.

Methods: FDA-defined registry success measures and other characteristics were collected from FDA's pregnancy registry website, product labels, publications, clinicaltrials.gov, and other Internet sources. Product

usage was estimated as market share using the 2013 IMS MIDAS data. As a proxy for awareness, the presence of registry information on website(s) (registry-specific, sponsor, or CRO) was assessed. Registry success was defined as achievement of at least one of the FDA-defined measures of success. Data were analyzed using logistic regression (SAS version 9.2).

Results: Of the 63 pregnancy registries identified, 11 (17%) achieved success. Factors significantly associated with success included registry duration (OR[10+ vs. <10 years] = 9.0; 95%CI: 2.1–38.8), websites (OR[>1 vs. ≤1] = 5.5; 95%CI: 1.3–23.4) and product market share (OR[above vs. below median] = 6.2: 95%CI: 1.2–31.8). While not statistically significant, registries with a broader scope (OR[global vs. single-region] = 3.3; 95%CI: 0.843–13.175) had higher odds of success.

Conclusions: This study built upon FDA's review and found registry duration, websites, and product market share to be associated with registry success. However, like FDA's evaluation, this study was limited in its ability to examine other potentially relevant factors.

470. First Data on Participation Rates of a National Pregnancy Drug Register in the Netherlands

Saskia Vorstenbosch, Agnes Kant. *Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands.*

Background: Approximately 80% of pregnant women use prescribed drugs. Information on potential risks of drug use for the fetus and women herself is limited, because pregnant women are normally not included in (pre-marketing) research. In the Netherlands, a national register is developed to systemically collect data on drug use during pregnancy and lactation and pregnancy-related outcome parameters.

Objectives: The aim of this study was to describe the initial results on participation rates of the national register pREGnant.

Methods: In pREGnant, pregnancies are monitored prospectively. Data are primarily collected through web-based questionnaires filled out by pregnant women, who are enrolled around their first prenatal care visit through their healthcare professional (HCP). An HCP could send an (e-mail) invitation and/or hand out a folder to notify pregnant women about pREGnant. Data collection points are <16 weeks, at 17 and 34 weeks gestational age and 2 and 6 months after delivery. The data collection started April 2014.

Results: Beginning of January 2015, 94 midwiferies have been approached, of which 32 agreed to participate in pREGnant (34% response). Sixteen of them agreed to send invitations, while 16 other midwiferies hand out or display the folder.

In total, 1240 women have received an (e-mail) invitation. It is estimated that approximately 1700 folders were distributed. The digital informed consent and first questionnaire were completed by 503 women, 407 of them had received an invitation (33% response), while 96 women had registered themselves, likely because they received the folder (6% response). Loss to follow-up of participants is low.

Conclusions: The systematic data collection in a pregnancy drug register like pREGnant will provide more insight on the safety profile of drugs used during pregnancy when large numbers of pregnancies are monitored. The initial results of pREGnant demonstrate that pregnant women are willing to participate and provide data through web-based questionnaires, especially when they are invited by their HCP. HCPs should therefore be encouraged to contribute to the register by attending pregnant women on its existence and the importance to participate.

471. Direct-to-patient Research: The Future of Pharmacovigilance?

Nancy A Dreyer,[1] Shahrul Mt. Isa,[2] Jonathan L Richardson,[3] Maja Laursen,[4] A Priscilla Zetstra-van der Woude,[5] Anna Jamry-Dziurla,[6] Valerie Hliva,[7] Alison Bourke,[8] Stella Blackburn.[9] *[1]Real World & Late Phase Research, Quintiles, Cambridge, MA, USA; [2]Imperial Clinical Trials Unit, School of Public Health, Imperial College, London, UK; [3]UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK; [4]Data Delivery & Medicinal Product Statistics, Statens Serum Institut, Copenhagen, Denmark; [5]Pharmacoepidemiology & Pharmacoeconomy, Pharmacy Dept, University of Groningen, Groningen, The Netherlands; [6]Medical Genetics, Poznan University of Medical Sciences, Poznan, Poland; [7]Real-World & Late Phase Research, Quintiles, St. Prex, Switzerland; [8]The Health Improvement Network, Cegedim Strategic Data, London, UK; [9]Real-World & Late Phase Research, Quintiles, Reading, UK.*

Background: Little is known about the effects of human fetal exposure when a new drug is authorized

unless specifically developed for use in pregnancy. Other factors may also contribute to adverse fetal effects, which then require evaluating a wide range of information to determine if causal relationship between a medication and an outcome exists.

Objectives: The aim of this study was to assess the extent to which women will provide useful information via the internet on some potential risk factors in pregnancy.

Methods: We conducted a prospective, non-interventional study of medication use and certain lifestyle factors during pregnancy to pilot a new method of pharmacovigilance as part of the PROTECT Consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium). Data were collected every 2 or 4 weeks from 2064 pregnant women in the United Kingdom (UK), Denmark (DK), the Netherlands, and Poland who were recruited by internet and leaflets in pharmacies. Self-reported prescriptions were compared with pharmacy register data in DK and with a sample electronic health records (EHR) in the UK.

Results: Women provided a substantial amount of information about prescription drug use, including medications used intermittently, use of non-prescription medications, herbals, and recreational drugs, and information about smoking and alcohol use. They also reported having used medication intended for someone else, not taking or discontinuing use of prescribed medication.

Conclusions: Overall, it appears that self-reported information on medication use, certain lifestyle factors, and pregnancy outcomes may provide some useful information for pharmacovigilance, but may not be sufficient, on their own, for research purposes. Self-reporting provides information that is not always available in EHR or pharmacy registers and which may differ from prescription data. When self-reported medication use did not match prescription data, it may reflect medications that were prescribed but not taken, poor compliance, or reluctance to self-report all medication used. Also, validation may be required to accurately characterize any birth abnormalities.

472. The Epidemiology of Ebstein's Anomaly in Europe: A Registry-based Study with Special Emphasis on Medication Exposure

Breidge Boyle,[1] Ester Garne,[2] Maria Loane,[1] Marie-Claude Addor,[3] Larraitz Arriola,[4] Clara Cavero-Carbonell,[5] Hermien EK deWall,[6] Miriam Gatt,[7] Nathalie Lelong,[8] Catherine Lynch,[9] Vera Nelen,[10] Amanda J Neville,[11] Mary O'Mahony,[12] Anna Pierini,[13] Anke Rissmann,[14] David Tucker,[16] Natalia Zymak-Zakutnia,[16] Helen Dolk.[1] *[1]Institute of Nursing and Health Research, Ulster University, Belfast, UK; [2]Paediatrics Department, Hospital Lillebaelt, Kolding, Denmark; [3]Division of Medical Genetics, CHUV, Lausanne, Switzerland; [4]Registro Anomalías Congénitas, CAV Subdirección de Salud Pública, San Sebastian, Spain; [5]Centro Superior de Investigación, Salud, Valencia, Spain; [6]Department of Genetics, University of Groningen, Groningen, The Netherlands; [7]Department of Health Information and Research, Guardamangia, Malta; [8]Paris Registry of Congenital Malformations, INSERM, Paris, France; [9]Health Service Executive, Kilkenny, Ireland; [10]PIH, Department of the Environment, Antwerp, Belgium; [11]Emila Romagna Registry of Birth Defects, Universitaria di Ferrara Corso Giovecca, Ferrara, Italy; [12]Health Service Executive, Cork, Ireland; [13]CNR, Institute of Clinical Physiology, Pisa, Italy; [14]Malformation Monitoring Centre, Saxony-Anhalt, Medical Faculty Otto-von-Guericke University, Magdeburg, Germany; [15]Congenital Anomaly Register and Information Service for Wales (CARIS), Public Health Wales, Swansea, UK; [16]OMNI-Net Ukraine Birth Defects Program, Khmelnytsky, Ukraine.*

Background: Ebstein's anomaly (EA) is a rare congenital malformation of the tricuspid valve and right ventricle of the heart. It has been associated with lithium and benzodiazepine exposure in pregnancy.

Objectives: The aim of this study was to describe the epidemiology of Ebstein's anomaly in Europe with reference to geographic and temporal variation in prevalence, associated malformations and syndromes, and risk factors including maternal age, parity, medical history, and medication exposure during pregnancy.

Methods: Descriptive epidemiologic analysis of data from 15 EUROCAT Congenital Anomaly Registries in 12 European countries covering a population of 5.6 million births in 1982–2011 was carried out. EA cases included livebirths, fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly (TOPFA). Prevalence rate per 10 000 births was calculated. Odds ratios (OR) for exposure to maternal illnesses and medications in the first trimester of pregnancy were calculated using logistic regression, by comparing EA cases to non-EA and

non-cardiac controls, excluding genetic syndromes. OR are adjusted for time period and country.

Results: The prevalence of EA was 0.47 (95%CI 0.41–0.53) per 10 000 births. Prevalence rose from 0.29 (95% CI 0.20–0.41) in the decade 1982–1991 to 0.55 (95%CI 0.46–0.67) in the decade 1992–2001 ($p < 0.01$). Cases were more likely to be exposed to maternal beta thalassemia adjOR 12.3 (95%CI 3.69–40.9, $n = 3$), hemorrhage in early pregnancy adjOR 1.74 (95%CI 0.91–3.33, $n = 11$), and insulin adjOR 3.41 (95%CI1.08–10.8, $n = 3$). Nine EA cases were exposed to maternal mental health conditions/medications adjOR 2.68 (95%CI 1.36–5.28), including seven who took antidepressants and four who took psycholeptics.

Conclusions: There is no evidence that EA is becoming more prevalent. Our data support previous literature concerning an association with mental health-related exposures. We find some new associations requiring confirmation.

473. Medication Use among Pregnant Women Enrolled in the United States Medicaid Program

Kristin Palmsten,[1] Sonia Hernández-Díaz,[2] Christina D Chambers,[1,3] Helen Mogun,[4] Sophia Lai,[5] Todd P Gilmer,[3] Krista F Huybrechts.[4] *[1]Department of Pediatrics, University of California, San Diego, La Jolla, CA, USA; [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [3]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, USA; [4]Division of Pharmacoepidemiology & Pharmacoeconomics, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA, USA; [5]Skaggs School of Pharmacy, University of California, San Diego, La Jolla, CA, USA.*

Background: Medication use during pregnancy among low-income women and variability in medication use by age and race/ethnicity are not well characterized.

Objectives: The aim of this study was to characterize the most commonly used prescription medications among pregnant women enrolled in Medicaid, the health insurance program for low-income individuals in the United States that covers >40% of deliveries in the country.

Methods: We identified 1 106 757 pregnant women with live births from 2000 to 2007 Medicaid Analytic eXtract (MAX) data. We used outpatient pharmacy records to identify medication dispensings. The most common medications were identified according to AHFS Pharmacologic–Therapeutic Classification class and medication name. Medication prevalences were stratified by maternal age and race/ethnicity and compared using prevalence ratios and 95% confidence intervals (CI).

Results: During pregnancy, 82.5% of the cohort had a dispensing for ≥1 prescription medication. The most prevalent classes included antibacterials (49.7%), analgesics and antipyretics (29.6%), and skin and mucous membrane anti-infectives (28.7%). There were differences in the prevalences of some of the most common classes across age and race/ethnicity groups. For example, compared with women ≥35, the prevalence of urinary anti-infectives was 1.5-fold higher (CI: 1.5–1.6), and antiprotozoals was 1.9-fold higher (CI: 1.8–1.9) during pregnancy among women who were <20. The antiprotozoal prevalence was 2.2-fold higher (CI: 2.2–2.3) among Black women compared with White women. The medications with the highest prevalence during pregnancy were nitrofurantoin (21.6%), metronidazole (19.5%), amoxicillin (18.0%), azithromycin (16.9%), and promethazine (13.5%). Excluding estrogens, progestins, and infertility treatments, 39.9% of women had ≥1 dispensing for a medication classified in the former Food and Drug Administration categories D or X. Codeine (13.0%) and hydrocodone (10.2%) had the highest prevalences of all D medications.

Conclusions: Prevalences of commonly used medications during pregnancy varied by age and race/ethnicity. The most prevalent prescription medications in pregnancy were for treating infections, particularly among younger women.

474. Medications Prescription in Pregnancy: Is There an Association with Sociodemographic Features?

Francesca Sammartano,[1] Silvia Ussai,[2] Liza Vecchi Brumatti,[3] Anica Casetta,[4] Federica E Pisa,[1,2] Fabio Barbone.[1,2,4] *[1]Department of Medical and Biological Sciences, University of Udine, Udine, Italy; [2]Institute of Hygiene and Clinical Epidemiology, University Hospital of Udine, Udine, Italy; [3]Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", Trieste, Italy; [4]*

Department of Medicine, University of Trieste, Trieste, Italy.

Background: In developed countries, between 27% and 99% of women have medications prescription during pregnancy. Sound evidence on medications safety in pregnancy is often limited.

Objectives: The aim of this study is to assess (a) the medications prescribed in each pregnancy trimester and (b) the association between having at least one prescription during pregnancy and selected sociodemographic features.

Methods: This cohort included pregnant women recruited at the first visit in a prenatal clinic in Friuli Venezia Giulia region, Italy, from 3 April 2007 to 3 March 2009. The women completed a self-administered questionnaire inquiring about gestational age, date of delivery, and sociodemographic features. For each woman, all prescriptions redeemed from 2006 to 2010 were extracted from the regional prescription database. Prescriptions from the date of conception to the date of delivery were considered during pregnancy. The odds ratio (OR), with 95% confidence interval (95%CI), of having at least one prescription during pregnancy was calculated through unconditional logistic regression.

Results: Of 767 women, 70.5% had prescriptions during pregnancy; 62.8% in the first trimester, 49.5% in second, and 57.5% in third.

Folic acid was the most prescribed agent in first ($n=200$, 58.8%) and second trimesters ($n=85$, 31.7%), while iron in third ($n=174$, 56.0%). Progesterone was often prescribed in first trimester ($n=90$, 26.5%) and antibacterials in second ($n=85$, 31.7%).

When simultaneously adjusting for country of origin, age, and education, the OR of having at least one prescription during pregnancy was 1.4 (95%CI 0.8–2.7) in immigrant versus Italy-born women, 1.3 (95%CI 0.7–2.6) in women aged 40–44 vs. 30–34 years, and 1.2 (95%CI 0.7–1.9) in women with schooling title <high school versus university.

Conclusions: Folic acid and iron were the most prescribed medications. About one-third of women had progesterone prescriptions in first trimester, likely for miscarriage risk. Antibacterials were prescribed mainly in second trimester. Immigrant women were 40% more likely to have prescriptions than those born in Italy.

475. Systematic Review of Pregnancy Exposure Registries: Fetal/Infant Outcomes, Target Sample Size, and Comparators

Kate Gelperin,[1] Hoda Hammad,[1] Steven Bird,[1] Christian Hampp,[1] Kira Leishear,[1] Leyla Sahin,[2] Lockwood Taylor.[1] *[1]Office of Pharmacovigilance and Epidemiology, FDA, Silver Spring, MD, USA; [2]Pediatric and Maternal Health Staff, FDA, Silver Spring, MD, USA.*

Background: Pregnancy exposure registries prospectively collect information on medical product exposure during pregnancy, including pregnancy outcomes and congenital birth defects. A 2002 FDA Guidance recommends that a written protocol pre-specify outcomes, provide sample size requirements based on study objectives, and identify appropriate comparison groups.

Objectives: Our study sought to systematically review and describe pregnancy registries based on prespecified fetal/infant outcomes, sample size calculations, and comparator selection.

Methods: We identified pregnancy registries using clinicaltrials.gov, the FDA Office of Women's Health pregnancy registry webpage, and the FDA Postmarket Requirement and Commitment database. Registries were included if they enrolled US patients, started before 2014, and were designed primarily to study medical product exposures in pregnancy. Rare disease registries and vaccines were excluded. For multidrug registries, a single-representative product was identified based on selection rules intended to minimize bias. We sought to obtain the study protocol for each included registry.

Results: A total of 36 unique pregnancy registries qualified for inclusion, of which 10 were multidrug registries. A primary outcome for all but two of the registries was overall major birth defects. Target enrollment was stated for 19 (63%) of the 30 registries, for which a protocol or similar documentation was available, and ranged from 200 to 800 exposed pregnancies (median 300). Statistical power to detect an increased risk of overall major birth defects with relative risks ranging from 1.39-fold to 3-fold (median 2.2-fold) was described for 20 registries. Most power calculations were based on a comparison with rates from the Metropolitan Atlanta Congenital Defects Program.

Conclusions: Most of the registries identified in this review were designed to assess the overall risk of major birth defects. Effects on less common, specific, birth defects may be missed for all but the most potent teratogens.

476. A Multidisciplinary Structured Approach for Interpreting and Integrating Medication Exposure and Pregnancy Outcomes Information

Keele E. Wurst,[1] Sara A. Ephross,[1] Patrick Wier,[2] Greta A. Bushnell,[3] Alice D. White.[3] *[1]Worldwide Epidemiology, GlaxoSmithKline, Durham, NC, USA; [2]Safety Assessment, GlaxoSmithKline, Upper Merion, PA, USA; [3]Epidemiology, University of North Carolina, Chapel Hill, NC, USA.*

Background: In December 2014, the US Food and Drug Administration (FDA) issued its final rule on labeling requirements for pregnancy and lactation mandating the inclusion of an integrated summary of all available information. We have developed and implemented an approach to interpreting and integrating information regarding the safety of medications in pregnancy. This methodology provides a framework for both pregnancy investigation and compliance with the new FDA rule.

Objectives: The aim of this study was to describe the activities of a multidisciplinary pregnancy outcomes advisory panel (POAP).

Methods: Traditionally within the pharmaceutical industry, no systematic process existed to interpret and integrate pregnancy outcomes information across the full spectrum of drug development. The POAP was formally established to provide expertise and develop a proactive, integrated approach for evaluation of pregnancy exposures and outcomes. The panel includes expertise from pre-clinical, clinical, safety, epidemiology, and regulatory.

Results: POAP delivers expert interpretation of all available animal and human pregnancy outcomes data using an objective, systematic, and integrated weight-of-evidence evaluation. All available evidence is collected, critically appraised, and assessed for study quality. Pharmacological, toxicological, and epidemiological considerations as well as the strength, consistency, specificity, and biological plausibility of potential associations are evaluated. The evaluation may conclude that there is sufficient information to be confident that there is no safety signal, or there is a positive association with a defined risk estimate, or recommend additional pre-clinical or clinical study, which may range from general exposure surveillance to formal hypothesis-driven epidemiology studies.

Conclusions: The systematic process of evaluation enables us to anticipate both current and future needs for pregnancy exposure/outcome investigation. Incorporating multidisciplinary evidence allows for an effective and comprehensive evaluation of pregnancy outcomes data. This structured approach may serve as a model system for implementing new FDA labeling requirements.

477. Performance of an Algorithm for Identifying Pregnancy Outcomes in Commercial Health Plan Claims Data

Wendy J. Carman,[1] Neil A. Accortt,[2] Li Zhou,[1] Lauren Sanders,[1] Mary S. Anthony,[3] Cheryl Enger.[1] *[1]Epidemiology, Optum, Ann Arbor, MI, USA; [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, USA; [3]Epidemiology, RTI-HS, Research Triangle Park, NC, USA.*

Background: There is increasing interest in using administrative data to examine pregnancy outcomes. The accuracy of using claims to identify particular pregnancy outcomes is not well known.

Objectives: The aim of this study was to assess the performance of an algorithm for identification of pregnancy outcomes within a commercial insurer's administrative database as compared with medical records.

Methods: In a retrospective study of pregnant women with psoriasis or chronic inflammatory arthritis and a general population comparator group, an 8.5% random sample of pregnancies, stratified by pregnancy outcome, was identified in a large claims database using systematic tracking of real kids, a process that identifies pregnancies and links mothers and babies in administrative claims. Outcomes for live births (single and multiple), non-live outcomes (stillbirth, spontaneous, and non-spontaneous abortions), and unknown outcomes were identified using a claims algorithm. Medical charts were sought and reviewed to confirm outcomes in claims. Positive predictive values (PPVs) and 95% confidence intervals (CIs) were calculated to estimate the proportion of claims that were true cases.

Results: Medical records were received for 300/457 pregnancies. Outcome data were recorded in the procured medical records for 180/232 live birth and 53/55 non-live birth claims. The PPV for claims-based live birth outcomes was 98.3% (95%CI: 94.8–99.6). All 53 charts for non-live outcome claims were confirmed as non-live [PPV = 100%, (95%CI:

91.6–100.0)]. Finer distinctions within these categories were also assessed. Among live births, the PPV for claims identifying single full-term live births was 97.2% (95%CI: 92.6–99.1), but for multiple live births, it was 18.8% (95%CI: 5.0–46.3). Among non-live births, the PPV for spontaneous abortions was 100% (95%CI: 86.0–100.0), but for non-spontaneous abortions, it was 23.1% (95%CI: 6.1–54.0) with 10/13 of those claims described in charts as spontaneous.

Conclusions: Our algorithm performed well in discriminating live and non-live pregnancy outcomes and in identifying spontaneous abortions but did not perform well for differentiating multiple live births or non-spontaneous abortions.

478. Performance of an Algorithm for Determining Dates of Conception and Pregnancy Termination Dates Using Commercial Health Plan Claims Data

Wendy J. Carman,[1] Neil A. Accortt,[2] Li Zhou,[1] Lauren A. Sanders,[1] Mary S. Anthony,[3] Cheryl Enger.[1] *[1]Epidemiology, Optum, Ann Arbor, MI, USA; [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, USA; [3]Epidemiology, RTI-HS, Research Triangle Park, NC, USA.*

Background: Use of administrative data to examine the relationship of exposures to pregnancy requires pregnancy start and end dates. Information regarding the accuracy of the use of claims to estimate of these dates is needed.

Objectives: The aim of this study was to assess the performance of an algorithm for identification of the pregnancy start and end dates within a commercial insurer's administrative database as compared to dates found in medical records.

Methods: In a retrospective study of pregnant women with psoriasis or chronic inflammatory arthritis, and a general population comparator group, an 8.5% random sample, stratified by pregnancy outcome, was identified from a large claims database using systematic tracking of real kids, a process to identify pregnancies and link mothers and babies in administrative claims. Medical charts were sought to validate outcomes and pregnancy dates. We identified a sample of 457 pregnancies, representing claims for 322 live births, 117 non-live births, and 20 unknown outcomes.

Results: Overall, 219 chart-based pregnancy end dates were available from the charts of 300 pregnancies for date validation. Of these, 216 (98.6%) had an end date within 34 days of the claims-based end date and 96.8% within 21 days. Pregnancy start dates were available in 266 charts where 240 (90.2%) were within 34 days of the claims-based conception dates and 229 (86.1%) were within 21 days. Pregnancy start dates within 21 days were validated for 100% of pre-term deliveries and 91.6% of single live births but were less accurate for abortions, ranging from 72.7% for elective to 79.3% of spontaneous abortions within 21 days and from 75.0% of ectopic pregnancies to 86.2% of spontaneous abortions within 42 days. Pregnancy conception dates for multiple live births were validated for 48.3% within 21 days to 86.5% within 42 days.

Conclusions: Overall, our dating algorithms performed well in identifying pregnancy end dates for most outcomes and in calculating conception dates for single live births. Further refinement may improve dating of early terminations, and further work is needed for pregnancies with multiple births.

479 .Prevalence and Associated Factors with Use of Medication during Pregnancy by Risk Class

Djanilson Barbosa Santos,[1] Bruna Cunha Girardi,[1] Lais Alves de Lima Prisco,[1] Wilanne Pinheiro de Oliveira Alves,[1] Michele de Jesus Cavalcante.[1] *[1]Centro de Ciências da Saúde, Universidade Federal do Recôncavo da Bahia, Santo Antônio de Jesus, Bahia, Brazil.*

Background: Drug use in pregnancy is often a reason of concern for mothers and their physicians. However, only few studies investigated predictors of drug use in pregnancy.

Objectives: The aims of the study were to describe drugs used and to identify the maternal determinants of the consumption of medication during pregnancy according to risk class.

Methods: We conducted a population cohort baseline cross-sectional study with 717 women in Bahia, Brazil. Information was obtained from interviews and prenatal cards. Medicines were classified according to the Anatomical Therapeutic Chemical Classification System of the World Health Organization and risk categories according to the US Food and Drug Administration.

Results: Of a total of 717 women, 619 (86.3%) used at least one drug during pregnancy, with a total of 1555 drugs used. The drugs most frequently used were vitamins associated with anti-anemics (85.4%), gastrointestinal drugs (31.3%), analgesics and anti-inflammatory drugs (25.7%), anti-anemics (19.8%), and antibiotics (11.1%). Regarding gestational risk, 997 drugs used (64.1%) belonged to category A risk, 291 (18.7%) to category B, 238 (15.3%) to category C, 20 (1.3%) to category D, and 9 (0.6%) to category X. The use of any medication showed a positive association with the beginning of prenatal care in the first trimester (PR = 1.16; 95%CI: 1.03–1.30), the economy class A/B (PR = 1.17; 95%CI: 1.06–1.29), and have any health problems (PR = 1.11; 95%CI: 1.05–1.18). The drugs that were used for anemia were associated with age less than 30 years (PR = 1.12; 95%CI: 1.01–1.24), early prenatal care in the first trimester (PR = 1.36; 95%CI: 1.11–1.58), and have any health problems (PR = 1.14; 95%CI: 1.05–1.25). Use of multivitamins drugs was positively associated with having more years (11 years) of schooling (PR = 4.32; 95%CI: 1.88–9.93), White women (PR = 1.84; 95%CI: 1.06–3.20), and economy class A/B (PR = 2.28; 95%CI: 1.19–4.37).

Conclusions: There is a need to educate and counsel women of child-bearing age, regarding the advantages and disadvantages of drug use during pregnancies, with special reference to alternative therapies and self-medication.

480. Optimizing the Value of Pregnancy Reports in a Drug Safety Database

Amanda Golembesky,[1] Dirk De Cuyper,[2] Laura Shaughnessy,[1] Maureen Cooney,[1] Kristel Luijtens,[2] Marie Teil.[3] *[1]UCB Biosciences, Inc., Raleigh, NC, USA; [2]UCB Pharma, Brussels, Belgium; [3]UCB Celltech, Slough, UK.*

Background: UCB Pharma pregnancy reports are obtained from spontaneous reports (including published literature), non-interventional studies, and interventional clinical trials. UCB trial protocols require women who become pregnant to stop study drug and withdraw from the trial, whereas a pregnancy report in a UCB non-interventional studies does not. Once a pregnancy is reported, it is followed per routine pharmacovigilance practices. Data are housed in the UCB drug safety database, which is designed for standard safety evaluations, rather than pregnancy research. This has traditionally hindered the safety database's use for pregnancy research.

Objectives: The aim of this study was to describe the process utilized to improve knowledge of outcomes in certolizumab pegol (CZP) pregnancy cases reported to UCB drug safety.

Methods: The UCB safety database was searched for pregnancy reports from start of product development to 1 September 2014. Pregnancy reports following maternal or paternal exposure to CZP were included; literature reports were excluded. Data on exposure, pregnancy dating, maternal comorbidities, and infant events were extracted from case reports by two separate reviewers; reconciliation for discrepancies was performed by a third independent reviewer when necessary. Prospective and retrospective pregnancy reports were analyzed. Pregnancy dating was based on available information and ranked according to reporting reliability. Earliest trimester of exposure was determined using the reported drug start and stop dates and corresponding pregnancy dates.

Results: The safety database search yielded 794 potential pregnancy reports; 625 were deemed to be CZP pregnancy exposures. Of those, 579 comprised maternal and 46 paternal exposure. Three hundred and thirty-nine maternal and 33 paternal exposures had documented pregnancy outcomes. Pregnancies with unavailable outcomes were more likely to be spontaneous reports, with no differences by country or indication compared to those with available outcomes. Earliest trimester of CZP exposure was discernable for approximately 70% of pregnancies with known outcome.

Conclusions: This project is an important initiative to optimize existing data from drug safety databases considering the well-known limitations of such reporting mechanisms.

481. Obstetric Complications Following Fertility Treatment—Disentangling the Role of Multiple Gestation

Anna S. Oberg,[1,2] Tyler J. VanderWeele,[1] Catarina Almqvist,[2] Sonia Hernandez-Diaz.[1] *[1]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [2]Department of Medical Epidemiology & Biostatistics, Karolinska Institutet, Stockholm, Sweden.*

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Background: Understanding the extent that multiple gestations mediate risk of obstetric complications following exposure to fertility treatment may provide etiological insights and assist clinical decisions concerning treatment strategies and pregnancy monitoring.

Objectives: Implementing a structural approach to mediation analysis, we aimed to (1) assess the association between treatment and adverse outcome independent of underlying infertility and (2) quantify that the extent associations are mediated by multiple gestation.

Methods: From the nearly 1 million pregnancies recorded in the Medical Birth Register between 1996 and 2006 in Sweden, we selected the 8% ($N = 84\,689$) that occurred after more than 12 months of trying to achieve pregnancy (i.e., self-reported infertility). Fertility treatments were identified from self-reports, general medical records, and procedural information from fertility clinics.

Results: Compared to pregnancies achieved spontaneously, those assisted by fertility treatment had higher odds of all studied complications except gestational diabetes and urogenital infections. Associations to placenta previa (OR, 2.31; 95%CI: 1.89–2.82) and placental abruption (OR, 1.77; 95%CI: 1.46–2.16) were almost entirely independent of multiple gestations. Conversely, multiple gestations mediated the majority (86% and 75%, respectively) of the associations to preterm birth (OR, 1.90; 95%CI: 1.78–2.02) and Cesarean (OR, 1.43; 95%CI: 1.34–1.49) and all of the modest association with preeclampsia (OR, 1.14; 95%CI: 1.06–1.22). Both direct and mediated pathways contributed to the remaining positive associations with chorioamnionitis, labor induction, and postpartum hemorrhage. Restricting exposure to assisted reproductive technologies only and evaluating primiparous and multiparous women separately yielded similar results.

Conclusions: Interventions to restrict the occurrence of multiples could diminish or greatly reduce risks of numerous obstetric complications following fertility treatment. Independent association with serious placental complications still suggests that all pregnancies achieved after fertility treatment should be monitored as high risk.

482. Asthma Medication Use Before and After the Onset of Type 1 Diabetes in Children and Adolescents: A Population-based Cohort Study

Fariba Ahmadizar, Anke-Hilse Maitland-van der Zee, Anthonius de Boer, Patrick Souverein, Hubertus Arets. *Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.*

Background: It has been reported that patients with type 1 diabetes (T1DM) have a decreased lung function. Studies on the association of T1DM and asthma in children show controversial results.

Objectives: The aim of this study was to quantify asthma medication use in children and adolescents with and without (reference cohort) T1DM 5 years before and after the onset of diabetes.

Methods: A population-based cohort study was conducted in the Dutch PHARMO Record Linkage System. All children (<19 years) with at least two insulin prescriptions between 1999 and 2009 were included in the T1DM cohort ($n = 915$). Up to four times larger reference cohort ($n = 3590$) with the same age and sex distribution was sampled from the PHARMO RLS.

Results: The 5-year prevalence rate of asthma medication use in the T1DM cohort was substantially higher (23.2%), with a peak in the first year, compared with the reference cohort (18.3%) after the onset of diabetes. In both cohorts, children aged 4 years and younger used asthma medication statistically significantly more frequent compared with children in ages of 5–9, 10–14, and 15–18 years before the onset of diabetes, 68.0% compared with 22.6%, 24.7%, and 27.0%, respectively, in the T1DM cohort and 54.3% compared with 25.4%, 21.3%, and 28.3%, respectively, in the reference cohort. After the onset of diabetes, these rates were 31.0%, 17.1%, 24.3%, and 28.0% in diabetic patients and 21.6%, 16.1%, 16.5%, and 22.3% in the reference cohort, respectively.

Short acting muscarinic antagonists were used more frequently in the T1DM cohort compared with the reference cohort after the onset of diabetes (5.5% vs 0.62%, $p < 0.001$). The incidence rate of asthma medication use was 2.5 times higher in the first year after the onset of diabetes compared with the reference cohort (46.3 vs 17.9 per 1000 person-years) but not in later years of follow-up.

Conclusions: T1DM was associated with statistically significantly higher prevalence and incidence rates of asthma medication use after the onset of type 1 diabetes, with a peak in the first year after the onset of diabetes.

483. Antibiotic Exposure and the Development of Pediatric Psoriasis: A Population-based Case–Control Study

Daniel B. Horton,[1,2] Frank I. Scott,[1,3] Kevin Haynes,[1,4] Mary E. Putt,[1] Carlos D. Rose,[2] James D. Lewis,[1,3] Brian L. Strom.[1,5] *[1]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Wilmington, DE, USA; [3]Division of Gastroenterology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [4]Clinical Epidemiology, HealthCore, Wilmington, DE, USA; [5]Rutgers Biomedical and Health Sciences, Newark, NJ, USA.*

Background: Antibiotics disrupt human microbiota and have been associated with pediatric autoimmune diseases. Literature has suggested a link between tetracycline use and psoriasis onset and activity in adults.

Objectives: We tested the hypothesis that antibiotic exposure was associated with incident psoriasis in children.

Methods: A nested case–control study of children followed from birth was performed in The Health Improvement Network, a population-representative medical records database from the UK. Children aged 1–15 years with newly diagnosed psoriasis were compared with age-matched and sex-matched controls randomly chosen from general practices with at least one case, excluding children with immunodeficiency, inflammatory bowel disease, and juvenile arthritis. The association between antibacterial antibiotics and incident psoriasis was determined by conditional logistic regression.

Results: A total of 845 eligible cases were identified in 3.1M person-years. After adjusting for country, socioeconomic deprivation, number of outpatient visits, and infections within the past 2 years, antibiotic exposure in the last 2 years was weakly associated with incident psoriasis (adj. OR: 1.2, 95%CI: 1.00, 1.5). However, infections of both skin (adj. OR: 1.5, 95% CI: 1.2, 1.7) and elsewhere (adj. OR: 1.3, 95%CI: 1.1, 1.6) had similar and modestly stronger associations with psoriasis in the same model. Untreated non-skin infections (adj. OR: 1.5, 95%CI: 1.3, 1.8), but not antibiotic-treated non-skin infections (adj. OR: 1.1, 95% CI: 0.9, 1.3), were significantly associated with psoriasis. Different classes of antibiotics and age of first antibiotic exposure were not associated with psoriasis. When considering a lifetime exposure window, the associations between psoriasis and both antibiotic exposure (adj. OR: 1.5, 95%CI: 1.2, 1.9) and skin infections (adj. OR: 1.4, 95%CI: 1.2, 1.7) were similar.

Conclusions: Infections are associated with the development of pediatric psoriasis, but antibiotics do not appear to contribute to that risk.

484. The Impact of Antibiotic Exposures Early in Life on Childhood Obesity

Frank I. Scott,[1,2] Daniel B. Horton,[2,3] Ronac Mamtani,[4] Dale Y. Lee,[5] Kevin Haynes,[2] James D. Lewis.[1,2] *[1]Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Rheumatology, Nemours A.I. duPont Hospital for Children, Thomas Jefferson University, Wilmington, DE, USA; [4]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [5]Department of Gastroenterology, Seattle Children's Hospital, Seattle, WA, USA.*

Background: The agricultural industry has utilized antibiotics for several decades in young animals to promote weight gain. Studies in humans thus far have yielded conflicting results.

Objectives: We aimed to assess the impact of antibiotic exposure in the first 2 years of life on the development of early onset obesity in childhood.

Methods: We performed a cohort study within The Health Improvement Network (THIN). Children registered within a THIN practice within 90 days of birth with a documented height and weight at 4 years ± 6 months were included. Those with reactive airway disease or severe combined immunodeficiency were excluded. Antibiotic use was quantified as the number of prescriptions before 2 years of age within THIN. Anti-parasitic agents served as a negative control. Obesity was defined as a BMI z-score of >2.34 for males and >2.25 for females. Logistic regression models were adjusted for maternal and concurrent sibling obesity, sex, decade of birth, Townsend score, and urban dwelling, with backwards elimination of non-significant covariates that did not modify the OR for antibiotics by $>10\%$.

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Results: A total of 21 744 children (51.1% male) were included. Of the patients, 15 707 (72.3%) were exposed to an antibiotic before age 2. The mean BMI *z*-score at 4 years was 0.48 (SD 1.21), and 5.6% of individuals were obese at 4 years. Antibiotic exposure (OR: 1.25, 95%CI: 1.10–1.42), maternal obesity (OR: 2.21, 95%CI: 1.83–2.67), and sibling obesity (OR: 2.25, 95%CI: 1.65–3.06) were associated with obesity. Sex, decade of birth, Townsend score, and urban dwelling were not associated with obesity in the multivariate model. After adjusting for maternal and sibling obesity, there was a dose–response between number of antibiotic prescriptions and obesity (1–2: aOR 1.11, 95%CI: 0.92–1.35; 3–5: aOR 1.50, 95% CI: 1.21–1.85; >5: aOR 1.71, 95%CI: 1.30–2.52). Anti-parasitic agents were not associated with obesity (OR: 0.89, 95%CI: 0.63–1.25).

Conclusions: Antibiotic exposure early in life is associated with a dose-dependent increased risk of early onset obesity at age 4, independent of maternal and sibling obesity.

485. The Extent of Off-label Use of Psychotropic Drugs for Danish Children and Adolescents: A Nationwide Study

Eva Skovslund Nielsen,[1] Maja Hellfritzsch,[1] Mette Nørgaard,[2] Torben Laursen.[1] *[1]Department of Biomedicine: Pharmacology and Clinical Pharmacology, Aarhus University Hospital, Aarhus University, Aarhus, Denmark; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus University, Aarhus, Denmark.*

Background: In recent years, use of psychotropic drugs has been increasing among children and adolescents in Europe and USA. Off-label prescription is a well-known phenomenon in paediatric care worldwide, and rates as high as 65% have been reported in general paediatric hospitals and may be even higher for paediatric use of psychotropic drugs.

To our knowledge, no prior studies have explored off-label prescribing rates of psychotropic drugs to Danish children.

Objectives: The aim of this study was to describe off-label rates for psychotropic drug prescriptions in Danish children and adolescents.

Methods: We identified all prescriptions for psychotropic drugs filled by children and adolescents under the age of 18 years, from 2006 to 2012 using the Register of Medicinal Product Statistics. From the Danish Civil Registration System, we obtained gender and dates of births of the children receiving these drugs. Through linkage to the Danish National Registry of Patients, which contains information on diagnoses and dates of all inpatient and outpatient contacts to Danish hospitals, we classified prescriptions as either on-label or off-label according to age and diagnosis. Information on drugs approval status was obtained from the Summary of Product Characteristics.

Results: We identified a total of 926.242 prescriptions (32.1% to girls and 67.9% to boys), which were filled by 72.697 children (44.0% girls and 56.0% boys) over the 7-year period. Mean age for first prescription was 11.4 years (SD 5.88) for girls and 9.8 years (SD 5.37) for boys.

Overall off-label rates ranged from 70.7% (69.3; 72.1) in 2006 to 57.4% (56.3; 58.6) in 2012 for prescriptions for girls and from 53.4% (52.1; 54.7) in 2006 to 43.0% (42.2; 0.43.9) in 2012 for prescriptions for boys. Time trends showed significantly declining rates over the 7-year period for prescriptions for both girls and boys ($p = 0.001$).

Conclusions: These preliminary data show high but declining off-label prescribing rates, which, however, are comparable with rates reported in other countries. New legislation regarding development of drugs for children may further reduce the rate in the future.

486. State-level Variation of Psychotropic Drug Utilization in Children with ADHD in the United States Using Multiple Disparity Measures

Xinyue Liu,[1] Paul Kubilis,[1] Regina Bussing,[2] Almut G. Winterstein.[1,3] *[1]Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA; [2]Psychiatry, College of Medicine, University of Florida, Gainesville, FL, USA; [3]Epidemiology, Colleges of Medicine and Public Health & Health Professions, Gainesville, FL, USA.*

Background: Children with attention deficit/hyperactivity disorder (ADHD) represent the largest pediatric population with high likelihood of psychotropic treatment (PT). Geographic variation of PT in children with ADHD deserves investigation to detect disparities in following evidence-based practice guidelines.

Objectives: The aim of this study was to evaluate state-level variation of PT utilization in children with ADHD using Medicaid Analytic eXtract (MAX) data in 26 US states from 1999 to 2006.

Methods: For each study year, we followed children aged 4–18 years from their first ADHD diagnosis for 1 year to ascertain filled prescriptions for the three most commonly used psychotropic drug classes: stimulants, antidepressants, and antipsychotics. We extended the follow-up time to 2 years to evaluate psychotropic polypharmacy defined as using ≥2 psychotropic drugs concomitantly. We used extremal quotient (EQ), χ^2-test, boot strapping of coefficients of variation (CV), and logistic regression to evaluate state-level variation.

Results: We identified 235 432 to 449 408 patients from 1999 to 2005 for the 1-year cohort and 195 933 to 360 782 patients from 1999 to 2004 for the 2-year cohort. The highest and lowest state-level annual prevalence and the range of EQ of PT across years were 88.4%, 57.7%, and 1.3–1.4 for stimulants; 16.0%, 48.1%, and 2.3–2.6 for antidepressants; 24.1%, 63.5%, and 2.0–2.6 for psychotropic polypharmacy; and 7.1%, 46.5%, and 3.3–4.3 for antipsychotics. Both χ^2-test and boot strapping of CV rejected the null hypothesis that the prevalence of each drug class or polypharmacy was the same across 26 US states ($p < 0.001$). In the logistic regression, state of residence had significant impact on psychotropic treatment after the adjustment for age, gender, race/ethnicity, foster care, disability, poverty, and year ($p < 0.001$).

Conclusions: There is a significant state-level variation in psychotropic drug and psychotropic polypharmacy prescribing in children with ADHD. Further research is needed to investigate the reasons leading to the variation.

487. Medication Errors among Paediatric Inpatients at a Rural Referral Hospital in Kenya

Christabel N. Khaemba,[1] Christabel N. Khaemba,[2] Eric M. Guantai,[2] Margaret O. Oluka,[2] Kipruto A. Sinei.[2]
[1]Medicines Information and Pharmacovigilance, Pharmacy and Posions Board (Ministry of Health), Nairobi, Kenya; [2]Pharmacology and Pharmacognosy, University of Nairobi, Nairobi, Kenya.

Background: Medication errors are any error in prescribing, dispensing, administration or monitoring of a drug and are an important cause of patient harm. Literature suggests that children experience medication errors up to three times more than adults do and have a much higher risk of severe outcomes from such errors.

Objectives: The aim of this study was to determine the incidences, types of medication errors and predictors of dosing error in the paediatric inpatient wards at a rural referral hospital.

Methods: The study design was an observational cohort of paediatric patients aged 0–5 years admitted at the Kisii Level 5 Hospital general paediatric ward and newborn unit between June and August 2014. It entailed the prospective review of treatment sheets and files upon admission and for a period of up to 1 month thereafter. Descriptive statistics was used to determine frequency, incidences, means and standard deviations. The relationships between predictor and outcome variables for dosing errors were computed using logistic regression (with significance set at p-value of 0.05 and 95% confidence interval).

Results: Of 405 treatment sheets and files reviewed, 307 contained at least one medication error yielding an overall medication error rate of 75.8%. The total number of medication errors observed was 1023, consisting of documentation errors; 73.9%, dosing errors; 8.8%, monitoring; 8.6%, errors; and 5.7%, timing errors. Among children observed with medication errors, they occurred frequently in male children (41.2%), children less than 1 year (45.9%) and those admitted to the general paediatric ward (48.4%). Antimicrobials contributed to the highest number of medication errors accounting for 40.2% of the total observed errors. Children receiving more than five medicines had over six times the odds of experiencing dosing errors (OR: 6.4; 95%CI: 2.7–15.1; $p < 0.001$). There was a 90% less risk of a dosing error with oral routes as compared to intravenous route ($p < 0.001$).

Conclusions: Incidence of medication errors was high among paediatric inpatients, with documentation and dosing errors being the most common. Number of drugs and route of administration were found to be important predictors of dosing errors.

488. Psychiatric Healthcare Utilization and Related Costs in Newly Diagnosed Individuals with Autism Spectrum Disorder (ASD) in Quebec (Canada)

Caroline Croteau,[1] Laurent Mottron,[2] Jean-Eric Tarride,[3] Marc Dorais,[4] Sylvie Perreault.[1] *[1]Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada; [2]Faculty of Medicine, University of Montreal, Montreal, QC, Canada; [3]Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada; [4]StatSciences, Inc., ND Ile-Perrot, QC, Canada.*

Background: The exponential increase of children diagnosed with ASD puts pressure on healthcare systems. Little is known on how psychiatric service use and associated costs evolve after diagnosis.

Objectives: The aim of this study was to characterize the temporal course of psychiatric healthcare utilization and related costs in a cohort of newly diagnosed ASD individuals.

Methods: Cohort was built using RAMQ databases. Newly diagnosed ASD subjects were selected (≥2 diagnoses ICD-9: 299.X, excl. 299.2) between January 1998 and December 2010. Cohort entry was date of first diagnosis confirmed by the absence of ASD diagnosis in previous 5 years. Subjects aged ≥26 years, without full RAMQ drug coverage for 5 years after cohort entry or not covered in the year preceding entry, were excluded. Demographic and clinical characteristics were done at cohort entry. Descriptive use of psychiatric healthcare medical visits, hospitalizations, and psychoactive drug use (anticonvulsants, antipsychotics, antidepressants, anxiolytics, ADHD drugs, anticholinergics, and lithium) was assessed during 5 years of follow-up. Mean costs per patient were estimated at the 1-year and 5-year periods. Bootstrap analyses were used to assess differences in costs between 1-year and 5-year follow-up.

Results: A total of 1227 subjects were identified (male: 80.3%; median age: 7 years). In the 1-year period after diagnosis, the mean number of psychiatric medical visits was 7.5 ± 14.6 with mean cost per patient of $653CAD (95%CI: 582–723); those values reduced to 2.1 ± 4.2 and $205CAD (175–235), respectively, at 5 years. Psychiatric hospitalization rate was 10.4% with mean cost per patient $9717CAD (7253–12 180) at year 1; the rate and cost reduced to 3.7% and $4259 CAD (2395–6123) at 5 years. Psychoactive drug utilization was initially present in 49.3% of subjects and increased to 53.2% at 5 years. Associated mean drug costs per patient increased from $622CAD (539–706) to $889CAD (786–991), in this time period.

Conclusions: While costs for psychiatric medical visits and hospitalizations decreased by more than half over 5 years, psychoactive drug costs rose by 43%. Long-term care and monitoring among the ASD population were discussed.

489. Stratification, Hypothesis Testing, and Clinical Trial Simulation in Pediatric Drug Development

Ann W. McMahon,[1] M Dianne Murphy.[1] *[1]Office of Pediatric Therapeutics, Food and Drug Administration, Silver Spring, MD, USA.*

Background: Pediatric drug development is plagued by small sample sizes, unvalidated clinical endpoints, and limited studies. A methodology is required for testing hypotheses related to the disease and drug response. Even with a small patient population, a clinical trial can provide valuable information if one thinks through assumptions and tests them prior to the study (clinical trial simulation).

Objectives: The objective is to review a clinical trial simulation (CTS) to determine whether stratification within the pediatric population could be used to (1) assess response to a pharmacologic intervention and (2) design future trials based upon published stratified disease data.

Methods: CTS was conducted using all of the data available on the drug for a pediatric indication using an established pediatric scoring system. A placebo model, and exposure–response model, and a dropout model were established for the data available. The future design CTS was conducted using Kawasaki Disease (KD), with divergent clinical phenotypes by age stratum and a historical study of coronary artery abnormalities (CAA) in KD. For KD, additional variables were incorporated based upon multiple meta-analyses of KD with and without coronary abnormalities. These primary variables were tested in CTS against responses to intravenous gamma globulin and salicylate-varying doses. CTS was performed using Pharsight Trial Simulator (Certara, Princeton, NJ, USA).

Results: For the pediatric drug development trial, CTS predicted a 97% probability (ANCOVA) of trial success, and sample size and fixed dosing significantly altered outcome. The CTS in KD incorporated <1 year olds with a duration of fever in the CAA+ cases that

was 9.1 ± 3.3 compared to 14.1 ± 10.4 in CAA+ patients >5 year olds.

Conclusions: CTS has been used in exposure–response, placebo, and dropout modeling in pediatric drug development. CTS also provides a valuable tool for hypothesis testing related to age-specific disease processes, such as KD, and response to intervention and outcomes during drug development.

490. Cardiovascular Medication Use and Cardiovascular Disease in Children and Adolescents with Type 1 Diabetes

Fariba Ahmadizar, Soulmaz Fazeli Farsani, Patrick Souverein, Anthonius de Boer, Anke Hilse Maitland-van der Zee. *Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.*

Background: It is well established that type 1 diabetes (T1DM) is associated with an increased risk of cardiovascular disease (CVD) that begins already in childhood. So far, no study has quantified cardiovascular (CV) medication's pattern in children and adolescents with T1DM and compared this with a group of children without diabetes.

Objectives: The aim of this study was to investigate the prevalence and incidence rates of CVD and medication use 5 years before and after the onset of T1DM in children and adolescents.

Methods: A population-based cohort study was conducted in the Dutch PHARMO Record Linkage System. All children (younger than 19 years) with at least two insulin prescriptions between 1999 and 2009 as a T1DM cohort ($n = 925$) and up to four times larger reference cohort ($n = 3591$) matched by age and sex distribution were identified. The prevalence and incidence rates of CV medication use were studied and compared by χ^2-test between the two cohorts from 5 years before until 5 years after the onset of T1DM (the index date in both cohorts).

Results: The 5-year prevalence rate of CV medication use in the T1DM cohort was substantially higher compared to the reference cohort both before and after the index date ((2.17% vs 0.97%, $p < 0.001$) and (9.19% vs 3.16%, $p < 0.001$), respectively). After the index date, ACE and HMG COA inhibitors were the most prevalently used CV medications among children with T1DM (2.01% and 1.51%, respectively). In the T1DM cohort, the highest incidence rate of CV medication use was observed in the first year after the index date (28.1 per 1000 person years). Furthermore, in this cohort, two cases were hospitalized due to cardiomyopathy and one for heart failure after the diagnosis of T1DM.

Conclusions: Children with T1DM were more likely to use CV medication in the years before and after the onset of diabetes (with a peak in the first year after the onset of T1DM). Furthermore, as to be expected in this age category, very low numbers of CV hospitalizations have been observed in the T1DM cohort after the index date.

491. Increased Use of Oral Anti-diabetic Medications in Dutch Children Mainly Driven By (Off-label) Metformin Use

Soulmaz Fazeli Farsani,[1] Patrick C. Souverein,[1] Jetty A. Overbeek,[2] Marja M. van der Vorst,[3] Catherijne A. Knibbe,[4] Ron M. Herings,[2] Anthonius de Boer,[1] Aukje K. Mantel-Teeuwisse.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands; [2]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [3]Department of Paediatrics, St. Antonius Hospital, Nieuwegein, The Netherlands; [4]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands.*

Background: Global prevalence of obesity and types 1 and 2 diabetes mellitus is increasing rapidly in children. Although insulin and metformin are the only anti-diabetic agents currently approved for children, other oral anti-diabetic drugs (OAD) are also used in this population. There are limited data available on the trends and patterns of pediatric OAD use.

Objectives: The aim of this study was to document long-term trends in OAD use among children in the Netherlands.

Methods: A population-based cohort study was conducted using the Dutch PHARMO Database Network. All children (<20 years old) with at least one OAD dispensing were identified, and the numbers of incident and prevalent OAD users (numerators) were calculated. Age-adjusted incidence (1999–2011) and

prevalence (1998–2011) rates of OAD use were calculated using denominator data from the Dutch Central Bureau of Statistics, and trends over time were assessed using joinpoint regression software. Indications for OAD use were studied in a subset by linking community pharmacy dispensing records to general practitioner data.

Results: In 2011, the overall age-adjusted incidence and prevalence rates of OAD use were 20.7/100 000 (95%CI, 19.2–22.1) person-years (PY) and 53.8/100 000 (95%CI, 51.5–56.1) children, respectively. From 1999 to 2011, the overall age-adjusted incidence increased by an average of 18.9% (95%CI, 4.5–35.2) per year. The incidence and prevalence rates of OAD use were higher among girls and older age categories (10–14 and 15–19 years old). The increase in OAD use among children was mainly driven by increased use of metformin. During the study period, metformin was the most frequently dispensed drug with 3148 dispensings (67.7%), followed by glimepiride (10.7%), tolbutamide (8.1%), and gliclazide (6.9%). Indications for OAD use were only reported for half of the children in the subset and included type 1 diabetes (41%), type 2 diabetes (33%), and overweight/obesity (20%).

Conclusions: Incidence and prevalence of OAD use in children substantially increased in the Netherlands, especially among older children and girls. The main indications for OAD use were types 1 and 2 diabetes and, to a lesser extent, overweight/obesity.

492. Metformin Prescriptions as a Proxy for Pediatric Type 2 Diabetes Burden

Ann M. McNeill,[1] Tongtong Wang,[1] Yong Chen,[1] Ravi R. Shankar,[1] Michael Sanderak.[1] *[1]Merck Sharp & Dohme Corp, Whitehouse Station, NJ, USA.*

Background: Metformin (MET) is approved for treatment of type 2 diabetes (T2D) and is a most commonly used oral anti-hyperglycemic agent in children and adolescents in the USA. As such, MET prescriptions (Rx) could be used as a proxy for T2D status in these populations; however, the extent of off-label use of MET in pediatrics is not well studied.

Objectives: The aim of this study was to estimate the annual prevalence of ≥1 metformin Rx among children and adolescents and calculate proportions with concomitant diagnoses of T2D, obesity, polycystic ovarian syndrome (PCOS), and other conditions.

Methods: Patients identified in a large US commercial claims database, Truven Health MarketScan®, aged 10–20 years with ≥1 metformin Rx during years 2009–2013 with ±6 months of continuous enrollment from the date of the index MET Rx were eligible for analysis. Prevalence proportions and 95%CI were calculated using Poisson regression. Diagnosis and procedure codes within ±6 months of the index MET Rx were used to identify T2D and other medical conditions.

Results: Over all years, 22 387 patients had ≥1 MET Rx. Of these, 80% were female, and 83% were 15–20 years of age. Annual prevalence proportions were consistent across years and for 2013 were 0.39 (0.36, 0.41) and 1.13 (1.27, 1.34) *p*/1000 for 10–14 and 15–20 age groups, respectively. Among patients with MET Rx, mutually exclusive proportions with concomitant diagnoses were PCOS alone (23%), obesity alone (12%), PCOS and obesity (7%), T2D alone (10%), T2D with PCOS or obesity, or both (8%), or other diagnoses (40%). Sensitivity analyses on the subset of patients with ≥2 MET Rx within a 6-month time window resulted in very similar results in terms of the higher prevalence in the older age group and the proportions with and without a concomitant T2D diagnosis.

Conclusions: Within a large US claims database, a minority of patients (18%) with ≥1 or ≥2 MET Rx had a diagnosis of T2D; the vast majority (~80%) had diagnoses of PCOS, obesity, or diseases/condition other than T2D, suggesting that off-label use of MET is very common in youth in the USA. Furthermore, the presence of metformin Rx as a proxy for T2D in youth may grossly overestimate the burden of the disease.

493. Antibiotic Prescribing for Children in General Practice and Adherence to Treatment Guidelines

Verica Ivanovska,[1,2] Karin Hek,[3] Aukje Mantel Teeuwisse,[1] Bert Leufkens,[1] Liset van Dijk.[3] *[1]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Faculty of Medical Sciences, University "Goce Delcev", Stip, The Former Yugoslav Republic of Macedonia; [3]NIVEL, Utrecht, The Netherlands.*

Background: Overall, 80% of antibiotics are prescribed in general practice, mainly for viral respiratory tract infections (RTI) in children, and often as broad-spectrum products. Yet, detailed information on adherence to RTI treatment guidelines for antibiotic prescribing in children is scarce.

Objectives: Our study explores antibiotic prescribing patterns for pediatric fever, ear, and respiratory infections in Dutch general practices. Our objective is to determine guideline adherence in antibiotic prescribing for different pediatric RTIs and choice of antibiotics.

Methods: We used data from electronic medical records from the NIVEL Primary Care Database 2010 for children up to 18 years of age. Our first outcome measure was whether or not the GP adhered to recommendations in the GP guidelines on whether or not to prescribe antibiotics for the child's diagnosis. The second outcome measure referred to whether or not the GP prescribed the preferred antibiotic in case of prescribing. Outcomes are defined as disease-specific RTIs incidence rates per 1000 person-years and percentage of disease episodes treated in line with guidelines.

Results: During 2010, most frequent pediatric RTIs in general practice were upper respiratory infections, acute otitis media (AOM), fever, bronchitis, and tonsillitis. ICPC episodes treated with antibiotics range from 16% (fever) and 18% (URTI) to 67% (strep throat) and 71% (pneumonia). Others fall between 50% and 60%, including AOM, sinusitis, tonsillitis, and bronchitis. First-line antibiotics were prescribed in 62% of pneumonia episodes treated with AB, 78% of bronchitis, and 84% of AOM. Even though phenoxymethylpenicillin is the recommended treatment for strep throat and tonsillitis, it has rarely been used; instead, other penicillins were mostly prescribed.

Conclusions: This study reports a stable and relatively low antibiotic use for pediatric RTIs in the Netherlands. Still, the evidence reveals two aspects for concerns, such as treatments of certain viral infections not in agreement with guidelines and the use of broader spectrum and new antibiotics.

494. Adherence to Index Therapy as a Predictor of Treatment Augmentation in Children and Adolescents Newly Initialized on Metformin Monotherapy

Mona Cai,[1] Til Stuermer,[1] Cynthia J. Girman,[2] Michael Kappelman,[3] Nina Jain,[4] Alan Brookhart.[1]
[1]Epidemiology, University of North Carolina Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC, USA; [2]CERobs Consulting, LLC, Chapel Hill, NC, USA; [3]Pediatrics, Division of Pediatric Gastroenterology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA; [4]Pediatrics, Division of Pediatric Endocrinology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA.

Background: In type 2 diabetes (T2DM), patients with inadequate glucose control may be prescribed adjunct therapies or dosage intensification

Objectives: The aim of this study was to examine whether poor adherence to initial metformin (MET) treatment plays a role in treatment augmentation or intensification in children and adolescents with T2DM

Methods: We identified a cohort of patients aged 8–18 years with at least 27 months of continuous health plan enrollment between 2001 and 2012 from a large US insurance claims database. Patients who filled MET but had no prescription in the 12 months prior and had at least one hemoglobin A1c (HbA1c) test performed during follow-up were selected. Follow-up ("titration period") began 3 months after a patient's first fill for a total duration of 12 months. Patients with a diagnosis code for type 1 diabetes, gestational diabetes, and polycystic ovary syndrome and related symptoms were excluded. The cohort was followed until the occurrence of an HbA1c test, and proportion of days covered (PDC) statistics was calculated for the 90 days prior to the test date. Patient outcomes in the 30 days after test date were categorized as (1) prescription for the same dosage as titration period or (2) prescription reflecting treatment augmentation (dose increase or additional oral hyperglycemic agent (OHA)). Patients without a prescription in the outcome window were excluded. All patients were followed until augmentation, switching to a different OHA class, or end of follow-up

Results: A total of 1142 patients contributed a total of 1594 records with a consistent median of two HbA1c tests occurring during follow-up for both outcome groups. A 90-day PDC was similar among patients who augmented treatment and those who refilled their baseline dosage, mean (std), and median (Q1, Q3) 90-day PDCs—79.6 (33.8) and 100 (66.7, 100) compared with 80.5 (33.2) and 100 (71.1, 100), respectively, $p = 0.37$.

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Conclusions: Our results suggest that poor adherence does not predict treatment augmentation.

495. Association between Antipsychotics and Risk of Epilepsy in Patients with Autism Spectrum Disorder in Taiwan

Chien-Chou Su,[1,3] Ching-Lan Cheng,[1,2] Yen-Kuang Yang,[3] Yea-Huei Kao Yang.[1,2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]School of Pharmacy, National Cheng Kung University, Tainan, Taiwan; [3]Department of Psychiatry, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: Epilepsy occurs frequently in patients with autism spectrum disorder (ASD). However, few studies explore whether use of antipsychotics (APs) is correlated with epilepsy attack in ASD patients.

Objectives: The aim of this study was to determine whether the use of APs associates with risk of epilepsy in patients with ASD.

Methods: We conducted a nested case–control study within a population cohort from Longitudinal Health Insurance Database 2000. The cohort included patients with under the age of 18 years who were newly diagnosed ASD (ICD-9 code 299) by psychiatrists during 1997–2008 and excluded patients who were diagnosed epilepsy prior to ASD. To avoid diagnostic uncertainty, patients who had at least two outpatient visits for ASD after the initial diagnosis. Cases were defined as patients who experienced first epilepsy during study period. Up to five controls were matched to each case upon age, sex, and year of cohort entry. Patients were deemed currently exposed if their last APs prescription is at least 1 month until the index date. Recent users are defined by last prescription that was beyond 30 days of index date and within 365 days of index date. Nonusers (reference group) were defined as no APs prescription within 365 days of index date. We estimate crude and adjusted odds ratios (OR) within 95% confidence intervals of the association between APs use and epilepsy by using conditional logistic regression.

Results: The cohort comprised 519 patients with ASD, of whom 37 had epilepsy during study period. The incidence of epilepsy was 12.74 per 1000 person-years in patients with ASD. The mean age at cohort entry was 7.94 years (standard deviation: 4.38), and 81% were male. Thirty-five per cent of cases and 15% of controls were prescribed APs with 365 days of index date. Adjusted OR versus reference group were as follows: for current users, 1.96 (95%CI: 0.58–6.69); for recent users, 1.41 (95%CI: 0.32–6.28).

Conclusions: The results of this study showed that APs use tended to be associated with risk of epilepsy in patients with ASD. Large cohort population or randomized trial is needed to identify the risk factors for epilepsy in ASD and to confirm the association between APs and epilepsy in patients with ASD.

496. Initial Prescription Medication for Children with Anxiety: Concordance with Evidence

Greta A. Bushnell,[1] Stacie B. Dusetzina,[2] Bradley N. Gaynes,[3] Scott N. Compton,[4] Alice D. White,[1] Til Stürmer.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC, USA; [2]Division of Pharmaceutical Outcomes and Policy, University of North Carolina at Chapel Hill Eshelman School of Pharmacy, Chapel Hill, NC, USA; [3]Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA; [4]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC, USA.*

Background: SSRIs are recommended as the first-line medication treatment for children with anxiety based on randomized controlled trials (RCT), but it is unknown if medications are prescribed concordant with this evidence.

Objectives: The aims of this study were to determine the initial prescription medication received and to describe psychotherapy use before medication initiation in children with diagnosed anxiety disorders.

Methods: We used Truven Health's Marketscan Commercial Claims and Encounters database. We included children (3–17 years) initiating medication to treat anxiety from 2005 to 2012 with a non-obsessive-compulsive disorder anxiety diagnosis (ICD-9-CM = 293.84, 300.0×, 300.2×, 309.21, 309.81, and 313.23) 30 days prior to their filled prescription. Initial medication regimens were assessed using records of dispensed prescriptions; any SSRI included SSRI mono-therapy and SSRIs filled the same day as another anxiety medication. We used log-binomial

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regression to estimate crude prevalence ratios (PR) between initiation on an SSRI and age, co-morbid depression diagnosis, anxiety diagnosis, and prior psychotherapy visits.

Results: Of 46 940 children who initiated prescription medication for anxiety, 75% initiated SSRIs (68% SSRI mono-therapy and 7% SSRIs in combination). Other children initiated benzodiazepines (10%), non-SSRI antidepressants (6%), beta-blockers (1%), or other anti-anxiety mono-therapy (7%). Approximately 1% initiated non-SSRI combination therapy. The majority of children (57%) had no psychotherapy visit 30 days before medication initiation; in children with ≥1 visit, the median number of visits was 2 (interquartile range: 1–3). Younger children (3–12 vs 13–17 years: PR = 1.08, 95%CI: 1.07–1.09), children with co-morbid depression (PR = 1.14, 1.13–1.16), and children with ≥1 psychotherapy visit (PR = 1.13, 1.12–1.14) were more likely to initiate SSRIs; variation also existed by anxiety diagnosis.

Conclusions: The majority of commercially insured children initiating prescription medication for anxiety received medication concordant with RCT evidence and treatment guidelines; however, 25% did not initiate on an SSRI, and over half had no recorded psychotherapy visit in the month before medication initiation.

497. Psychotropic Medication Use Prior to Initiation of Antipsychotics in Foster Care Youth: Are All New Users Equal?

Wendy Camelo Castillo,[1] Ming-Hui Tai,[1] James F. Gardner,[1] Susan dosReis.[1] *[1]Pharmaceutical Health Services Research, University of Maryland, Baltimore, MD, USA.*

Background: Youth in foster care are more likely to be managed with psychotropic medications (PM), in particular antipsychotics (AP), than other Medicaid youth. APs are used mainly off-label in children with severe behaviors, but differences in prior PM use and associated outcomes among new AP users are unknown.

Objectives: The aim of this study was to characterize AP initiators and identify subgroups based on PM use prior to initiation. Risk of hospitalizations or emergency room (ER) visits across specific subgroups was also assessed.

Methods: A retrospective cohort of Medicaid-insured youth, <21 years, in foster care for at least 1 year during 2010–2014, from a mid-Atlantic US state was identified. Demographics and foster care placement data were obtained from the Child Welfare Administrative Database linked to Medicaid claims. AP initiators had no AP use in the prior 6 months. Other PM use was classified as attention-deficit/hyperactivity disorder (ADHD) treatments, antidepressants, and mood stabilizers and characterized by number of treatment changes (adding, switching, or discontinuation) and cumulative use (in days) for a given class. Hazard ratios (HR) and 95%CI were estimated using Cox proportional hazards model, adjusting for demographics and number of mental health diagnoses.

Results: We identified 259 AP initiators (mean age, 14 years; Black, 67%; and no PM in prior year, 38%). Relative to PM users, non-PM youth were younger (30% vs 27%, <10 years old), were male (61% vs 48%), had ≤2 mental health diagnoses (60% vs 47%), and had a lower percentage of ER visits (12% vs 15%) prior to AP initiation. Among prior PM users, 63% ($n = 73$) had ≤2 treatment changes during baseline. The median cumulative use of two or three PMs was 151 and 58 days, respectively. The risk of first hospitalization after AP initiation was lower among non-PM user compared to PM users (HR: 0.6; CI: 0.3–1.1) but similar for ER visits (HR: 1.0; CI: 0.4–2.3).

Conclusions: AP initiators had heterogeneous profiles with subgroup differences in outcomes risk. Accounting for PM patterns prior to AP initiation may clarify for whom treatment is most effective.

498. The Use of Psychotropic Medications in Autism Spectrum Disorder: The Parents' Perspective

Danielle Boucher,[1] Hubert Gascon,[1] Caroline Sirois,[1,2] Maude Garant.[1] *[1]Universite du Quebec a Rimouski, Levis, QC, Canada; [2]Centre d'excellence sur le vieillissement de Quebec, Quebec City, QC, Canada.*

Background: Although there is little evidence-based information about the efficacy and safety of psychotropic medication in young individuals with autism spectrum disorder (ASD), about half of this population uses psychotropic drugs. There is a need to better understand the parents' experience in relation to their decision to medicate their child.

Objectives: The aim of this study was to describe the parents' perspective regarding the use of psychotropic medication by their child with ASD.

Methods: We performed a qualitative study among 27 parents who have a child aged 9–16 years with ASD without intellectual disability. We performed semi-structured individual phone interviews to describe the parents' experience regarding the use of psychotropic medication by their child. Psychotropic medication included stimulants, antipsychotics, mood-stabilizers, antidepressants, and hypnotic-anxiolytic drugs. To study the parents' decision to give (or not) their child a psychotropic medication, we used Aizen's theory of planned behavior. We identified three types of perceptions: benefits/disadvantages of psychotropic medications, enablers/barriers of using medications, and the approval/disapproval of the relatives.

Results: Although most parents are satisfied with the drugs positive effects, some of them had to discontinue their child's medication due to side effects. Fear of side effects remains a major issue for all parents. Enablers that facilitated the decision to medicate the child included the presence of disruptive behaviors and the availability of medical support. Most parents perceive that there are more significant individuals in their life that agree with their decision to medicate their child than individuals who do not.

Conclusions: The results of this study better inform health professionals about the parents' expectations and concerns regarding the use of psychotropic medication in their child with ASD. Side effects remain the principal obstacle and disadvantage to medicating a young individual with ASD.

499. Modeling the Complexity and Continuity of Psychotropic Use among Youth as an Indicator of Illness Severity

Susan dosReis,[1] Wendy Camelo Castillo,[1] James Gardner,[1] Ming-Hui Tai.[2] *[1]Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD, USA; [2]PHARMetrics International, Bethesda, MD, USA.*

Background: Despite the low prevalence of schizophrenia and bipolar disorder in youth, antipsychotic use, generally prescribed for these conditions, has increased sixfold in the last decade among youth in publicly funded programs. Little work has been done to examine indicators of underlying severity of illness as a factor contributing to increased use. The goal of this study was to investigate psychotropic treatment patterns prior to initiation of antipsychotic medication.

Objectives: The aims of this study were to examine psychotropic sequencing prior to antipsychotic initiation and to investigate the stability of psychotropic treatment, in terms of therapeutic class switching and polypharmacy.

Methods: A new user design identified youth <20 years old among 18 034 youth in one state foster care system who initiated an antipsychotic from January 2010 to March 2014. Medicaid claims data and foster care records were used for this study. Treatment sequencing was examined over twelve 30-day periods prior to the index antipsychotic. Psychotropic treatment included four therapeutic classes that account for >90% of use in youth: attention-deficit/hyperactivity disorder (ADHD) medications, antidepressants, mood stabilizers, and antipsychotics. Concomitant therapeutic class use was defined as ≥15 days in a 30-day period.

Results: New antipsychotic users were on average 14 years old and 52% male. In the 30 days prior to antipsychotic initiation, 60% had no psychotropic use, 29% received one psychotropic, and 12% were using >1 psychotropic. Of those not taking psychotropic medication, 57% remained on no psychotropic medication the entire year. By comparison, 29% of antidepressant users, 21% of ADHD medication users, and 20% of mood stabilizer users remained on these medications the entire year. Switching was frequent; 60–80% experienced at least one treatment change in the year prior to the index antipsychotic.

Conclusions: Time-varying psychotropic patterns preceding antipsychotic initiation can be suggestive of underlying severity. Measures for psychotropic complexity are needed to improve characterization of risk profiles for health outcomes.

500. The Association between Atopic Diseases and Childhood Attention-Deficit/Hyperactivity Disorder: A Retrospective Matched Case–Control Study

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Jurjen van der Schans,[1] Janine C. Pleiter,[1] Tjalling W. de Vries,[2] Catherina C. M. Schuiling-Veninga,[1] Jens H. J. Bos,[1] Pieter J. Hoekstra,[3] Eelko Hak.[1] *[1]Pharmacy, Pharmacoepidemiology & Pharmacoeconomics, University of Groningen, Groningen. The Netherlands; [2]Medical Centre Leeuwarden, Leeuwarden, The Netherlands; [3]Psychiatry, University Medical Centre Groningen, Groningen, The Netherlands.*

Background: Data on the association between attention-deficit/hyperactivity disorder (ADHD) and atopic diseases have been inconclusive.

Objectives: We assessed whether children with ADHD are more likely to have a history of atopy like asthma, allergic rhinitis or eczema than children without ADHD.

Methods: A retrospective nested case–control study among children (6–12 years) using the IADB.nl prescription database was preformed. Medication proxies were used for the identification of ADHD and atopy. Cases were defined as children with at least two prescriptions of methylphenidate within 12 months. Cases were matched to four controls: patients without ADHD medication, on age, sex and area code. For each case and control, we recorded the presence of asthma, allergic rhinitis and eczema in the 3 years prior to the inclusion. Asthma was defined as having at least three prescriptions of an inhaled corticosteroid or a short working betamimetic, allergic rhinitis was defined as having at least three prescriptions of a corticosteroid for nasal use and eczema was defined as having at least three prescriptions of ointments containing steroids or at least three prescriptions of calcineurin inhibitors, all within 12 months. We further assessed the parental ADHD and atopic diseases as a predicting parameter on developing ADHD in childhood. Conditional logistic regression analysis was applied to obtain odds ratios (OR) and corresponding 95% confidence intervals (CI).

Results: We identified 4257 cases and 17 028 controls. Asthma, allergic rhinitis and eczema were more common in cases than controls with odds ratios of 1.4 (95%CI: 1.3–1.6), 1.4 (95%CI: 1.1–1.8) and 1.3 (95%CI: 1.1–1.5), respectively. Association of parental use of medication for atopy on receiving ADHD medication in the offspring (OR: 1.1; 95%CI: 1.0–1.2) was higher in cases compared to controls.

Conclusions: This study suggests that atopic diseases are associated with the development of ADHD. Future studies should focus on the genetic component of the association to clarify the possible underlying mechanism.

501. High Incidence of Oral Corticosteroids Prescriptions in Young Children with Asthma

Ali Arabkhazaeli,[1] Susanne J. H. Vijverberg,[1] Cornelis K. van der Ent,[2] Jan Raaijmakers,[1] Anke-Hilse Maitland-van der Zee.[1] *[1]Utrecht Institute of Pharmaceutical Sciences Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands; [2]Department of Pediatric Respiratory Medicine, University Medical Centre Utrecht, Utrecht, The Netherlands.*

Background: The prevalence of oral corticosteroid (OCS) use in children with asthma has been investigated in previous studies; however, there were no studies investigating age-categorized incidence of OCS use and the risk of subsequent prescriptions.

Objectives: We assessed the incidence in different age groups and also assessed the risk to receive a second or third OCS prescription.

Methods: In this retrospective study, we investigated the incidence of OCS prescriptions in 2206 Dutch children (age: 4–12 years) with respiratory symptoms using longitudinal anonymized pharmacy records from the PACMAN cohort study. All children were regular users of asthma medication. We assessed the incidence rates for first, second, and third prescriptions of OCS stratified by age and gender. The probability of receiving a first, second, or third OCS prescription during follow-up has been assessed with Kaplan–Meier analysis.

Results: The incidence rates of OCS prescriptions in the first and the second years of life were 4.6 (95% CI: 3.6–5.7) and 3.9 (95%CI: 3.1–4.9) per 100 person-years (PY), which was relatively high in comparison with the incidence rate for children between 6 and 10 years old (1.9 [95%CI: 1.0–3.4] to 2.7 [95%CI: 1.7–4.1] OCS prescription per 100 PY). Moreover, the incidence rates for second and third OCS prescriptions were very high (respectively 98.7 [95%CI: 60.3–152.4] and 181.0 [95%CI: 66.4–393.9] per 100 PY) for infants. The chance of receiving a first OCS prescription was different between boys and girls ($p < 0.01$). Boys had a higher chance of receiving OCS at all ages. In the whole population, the probability of getting a second or third OCS prescription in the

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2 years after first or second OCS prescriptions was 42.0% and 47.4%, respectively.

Conclusions: The incidence of OCS prescriptions in the children treated with asthma medication is relatively high for first OCS prescriptions and extremely high for second and third OCS prescriptions in early childhood. Furthermore, there is a high probability of receiving another OCS prescription shortly after an OCS prescription.

502. Comparative Safety of Antimuscarinics in the United States Pediatric Population, 2000–2012

Alan C. Kinlaw,[1] Jennifer M. Wu,[2,3,4] Mitchell M. Conover,[1] Michele Jonsson Funk.[1,3] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]Center for Women's Health Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [4]Center for Aging and Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Antimuscarinics are primary pharmacotherapy for overactive bladder, and prescribing to children and adolescents has increased in recent years with high occurrence of off-label prescribing. Comparative safety data in this population are limited.

Objectives: The aim of this study was to compare the incidence of constipation diagnosis codes among new users of antimuscarinics in the pediatric population.

Methods: Using longitudinal healthcare claims in Truven Health Analytics' MarketScan databases from 2000 to 2012, we identified new users of antimuscarinics among children under 18 years of age.

We excluded those with a constipation diagnosis code in the prior year and those with any diagnosis code for dry mouth, intestinal malabsorption, rectosigmoid junction, or malignant gastrointestinal neoplasm. We defined the outcome as at least two ICD-9-CM diagnosis codes for constipation within 1 year and assigned event times based on the first observed diagnosis date.

We used Kaplan–Meier curves to estimate cumulative risks and Cox proportional hazards models to estimate sex-specific hazard ratios (HR) and 95% confidence intervals (CI), adjusted for age, year, and region. Children were censored when their insurance provider or status changed.

Results: There were 27 714 eligible, new users of antimuscarinics. Fifty-six per cent were female, and median age at prescription was 8 years (interquartile range: 5–12). Ninety-six per cent were treated with oxybutynin or tolterodine. The 1-year cumulative risk for having two constipation diagnosis codes was 3.0% for girls (95%CI: 2.7–3.3%) and 2.1% for boys (95%CI: 1.8–2.3%). Incidence of constipation diagnosis codes was similar comparing IR to ER drugs among girls (HR: 0.92; 95%CI: 0.72–1.17) and boys (HR: 0.90; 95%CI: 0.66–1.24). Comparing oxybutynin to tolterodine, incidence of constipation diagnosis was also similar among girls (HR: 1.08; 95%CI: 0.77–1.53) and boys (HR: 0.85; 95%CI: 0.56–1.30).

Conclusions: For both girls and boys, we found similarities in incidence of constipation diagnosis codes across antimuscarinic treatment types.

503. Parental Exposure to Folic Acid Antagonists Is Associated with Childhood Cancer

Yu-Hsuan Joni Shao,[1,2] Ming-Tsang Chuang,[2] Kitaw Demissie.[3] *[1]Graduate Institute of Biomedical Informatics, Taipei Medical University, Taipei, Taiwan; [2]School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan; [3]Department of Epidemiology, School of Public Health, Rutgers University, Piscataway, NJ, USA.*

Background: Epidemiologic data and evidence from animal studies suggest that paternal exposure may influence the health of the fetus by transmission of environmental information through the sperm's epigenome.

Objectives: The aim of this study was to examine whether paternal exposure to folic acid antagonists is associated with increased risk of childhood cancer.

Methods: A retrospective population-based cohort study was conducted utilizing the Taiwan Linked Parental–Child Database from 2004 to 2007 (N= 418 068). The database links the Taiwan Birth Certificate Registry (TBCR) with the Taiwan National Health Insurance Research Data (NHIRD). NHIRD contains all medical claims as well as registry files of contracted medical facilities of providers.

Results: Among the 418 068 infants, the parents (either father or mother) of 25 357 were prescribed some kind of folic acid antagonists (antibiotics, anti-inflammatory medications, NSAIDs, and others) during periconception or pregnancy. The average follow-up is 3.93 years (SD 1.26). The cumulative incidence of cancer among children with no parental exposure (neither father nor mother, the reference) was 276 per million [95% confidence interval (CI): 213–351]. The cumulative incidence associated with only paternal exposure [251 per million (95%CI: 149–397)] was almost the same or a bit lower than the reference value. Only maternal but not paternal exposure was associated with significantly higher cumulative incidence [402 per million (95%CI: 367–439)] than the reference. Both maternal and paternal simultaneous exposure did not substantially alter the cumulative incidence to that obtained from maternal exposure only. The adjusted hazard ratios were 1.67 (95%CI: 1.14–2.45) for both maternal and paternal exposure, 1.60 (95%CI: 1.24–2.08) for only maternal exposure, and 0.97 (95%CI: 0.58–1.64) for only paternal exposure. The observed effect was stronger in boys than in girls (aHR 2.04 vs 1.24) and in developing embryonal tumors than other type of tumors (aHR 2.63 vs 1.67).

Conclusions: The findings of this study provide evidence that maternal exposure to folic acid antagonists during periconception and pregnancy is associated with increased risk of childhood cancer.

504. Access to Oral Paediatric Medicines in Ghana: An Unmet Need

Daniel Ankrah,[1,2] Joseph Turkson,[2] Edith Boateng,[3] Frank Amegavie,[2] Elizabeth Bruce.[2] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Pharmacy Department, Korle-Bu Teaching Hospital, Accra, Ghana; [3]School of Pharmacy, University of Ghana, Accra, Ghana.*

Background: Off-label prescription of paediatric medicines has been reported to be associated with unknown adverse reactions. Even though the Ghana National Drugs Programme has accepted the World Health Organization's priority medicines list for children and maternal health as a working document, having the medicines list is necessary but not sufficient to guarantee treatment.

Objectives: This study identifies frequently prescribed children's medicines that are not readily available as pre-formulated preparations in Ghana and are prepared extemporaneously and makes recommendations for the way forward.

Methods: In this study, data were collected prospectively. All prescriptions for extemporaneous oral preparations for children 9 years and below presented to the local production unit of the Korle-Bu Teaching Hospital from November 2013 were eligible for the study. Information from such prescriptions was recorded in a systematic format. The date, treatment centre, patient's name and sex, age, name of preparation and patient reported morbidity were recorded. The presence of the prescribed medicine on the World Health Organization Children' Medicines List and registration of the prescribed medicine for paediatric use by the Food and Drugs Authority Ghana were ascertained. Descriptive statistics of the data were presented.

Results: The total number of prescriptions captured was 622, and the most distant treatment centre was located 616 km away from the Korle-Bu Teaching Hospital. Prescriptions from several health facilities including government hospitals, private hospitals and the University of Ghana Hospital were all honoured. Some of the prescribed medicines were neither on the World Health Organization Children's Medicine list nor registered with the Food and Drugs Authority Ghana. The most prescribed medicines were for management of cardiovascular diseases and seizures.

Conclusions: Steps should be taken by policy makers and all involved to improve access and monitoring of benefit-risk profiles of these medicines in order to promote better treatment outcomes among paediatric patients.

505. Use of Epidemiology Data to Inform Pediatric Clinical Trials

Laura E. Wallace,[1] Stacy Baldridge.[1] *[1]Purdue Pharma LP, Stamford, CT, USA.*

Background: Recruitment of rare patient types into clinical trials (CT) is a challenge; epidemiology data can be used to improve this process.

Objectives: The aim of this study was to demonstrate the use of epidemiology (epi) to provide targeted data for a pediatric CT, particularly for site and investigator

identification, feasibility assessment, and Medical Science Liaison (MSL) support.

Methods: We conducted a retrospective cohort study of pediatric patients with persistent pain using Marketscan claims data from the USA. Data informed CT design, investigator recruitment, and trial support. We collected feedback on the data's usefulness from MSLs and CT staff.

Results: The cohort study included 25.5 million pediatric patients in the USA. Of the patients, 8.7% had a pain diagnosis, but few had persistent pain, and most did not receive prescription pain treatment. Opioids were used in 17.7% of pediatric patients with pain conditions, NSAIDS in 7.5%, and anticonvulsants in 2.0%. The types, doses, and duration of treatments varied substantially by condition and age.

We used these data to inform decisions about CT design, investigator and site selection, and MSL support. Findings enhanced site interactions through clinical discussions of painful conditions and treatments. A targeted initiative for surgical and orthopedic populations was implemented to expand recruitment based on data showing the prevalence of children requiring pain treatment at study-relevant doses and timeframes. Activities to identify practitioners and specialty centers were undertaken based on data that contributed to understanding enrollment potential.

Conclusions: With a broad range of potential investigators crossing multiple specialties, identification of CT sites for pediatric pain studies is challenging. By targeting efforts based on data from epi studies, sites may be evaluated in greater detail. MSL support of CTs includes initial site identification, protocol education, and patient advocacy organization interaction. Data collected from epi studies provide the MSL with clinically relevant data to enhance subject recruitment and engage in outreach to additional groups, contributing to improved CT processes.

506. The Risk of Malignancy among Biologic-naïve Pediatric Psoriasis Patients: A Retrospective Cohort Study in a US Claims Database

Yun Gu,[1] Beth L. Nordstrom.[2] [1]*Pfizer, Collegeville, PA, USA;* [2]*Evidera, Lexington, MA, USA.*

Background: There is a paucity of published literature on the risk of development of malignancy in pediatric psoriasis.

Objectives: The aim of this study was to compare the risk of malignancy in biologic-naïve patients with pediatric psoriasis with a matched pediatric population without psoriasis among commercially insured individuals in the USA.

Methods: This retrospective cohort study used data from the IMS LifeLink™ Health Plan Claims Database from 1998 to 2008. Patients diagnosed with pediatric psoriasis were identified, and up to 10 matched comparators without psoriasis were selected for each psoriasis patient. Incident cancer was determined using ICD-9 codes, procedures, and treatment from the claims data via clinician profile review. Standardized incidence ratios (SIR) compared the incidence rates in each cohort with general population rates in SEER. The risk of cancer in pediatric psoriasis and comparator patients was compared using Cox proportional hazards regression.

Results: A total of 9051 patients with pediatric psoriasis and 77 262 matched comparators were included. One pediatric psoriasis patient and 17 comparators had claims judged to be probable or highly probable cancer after 90 days from cohort entry (mean follow-up: 19 months). Incidence rates of cancer were 5.42 (95%CI: 0.00–16.04) and 10.52 (95%CI: 5.52–15.52) per 100 000 person-years for pediatric psoriasis and comparators, respectively. The risk of cancer in pediatric psoriasis was nonsignificantly lower than comparators (HR = 0.52; 95%CI: 0.07–3.94). Inclusion of cancer diagnosed during the first 90 days of follow-up after entry increased the HR to 1.68 (95%CI: 0.58–4.91). The pediatric psoriasis cohort had an elevated rate of lymphoma compared to SEER (SIR = 5.42, 95% CI: 1.61–12.94) and to the matched comparator cohort (HR = 7.23; 95%CI: 1.18–44.26).

Conclusions: Patients with pediatric psoriasis showed no significant elevation in risk of any cancer compared to those without psoriasis, but they may be at increased risk of lymphoma. Further investigation is warranted in larger populations of pediatric psoriasis patients with longer follow-up.

507. Factors Associated with Hospital Admissions through the Emergency Department for Pediatric Patients with Acute Asthma

Wei Wang,[1] Haesuk Park.[1] [1]*Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA.*

Background: Asthma attacks remain a frequent cause of presentations to emergency departments and of admissions to hospital among pediatric patients. However, little is known about the incidence and factors of inpatient admissions through the emergency department (ED) for pediatric patients with acute asthma.

Objectives: The aims of this study were to identify factors associated with unscheduled admissions to the hospital after the ED visits among children with acute asthma and to compare the rate of hospital admissions through the ED between Medicaid-insured and privately insured asthmatic children.

Methods: A retrospective analysis using 2010–2011 National Emergency Department Sample (NEDS), the largest all-payer hospital-based ED database in the USA, was conducted. All ED visits with a primary diagnosis of acute asthma for patients aged 2–17 years were identified using ICD-9-CM codes of 493.XX. ED visits with unknown destination were excluded. Multivariate logistic regression and generalized linear mixed model were used to identify risk factors and examine insurance-related difference of hospital admissions through ED among asthma children.

Results: A total of 110 964 pediatric asthma-related ED visits from 1713 US EDs was identified (Medicaid patients: $n = 69\,410$ (63%), mean age = 7 years, 39.86% female; privately insured patients: $n = 41\,554$ (37%), mean age = 7 years, 39.79% female). Of these occurrences, 96 307 (87%) were discharged, and 14 657 (13%) were admitted to hospital after ED visits. Factors associated with hospital admissions through the ED were younger age, male, severity, insurance type, weekday visits, visit season, and region, location, and ownership of hospital. After adjusting for demographic and clinical factors, private insurance was associated with a 22% increase in the odds of hospital admissions through ED compared to Medicaid (odds ratio = 1.22, [95% confidence interval: 1.13–1.32]).

Conclusions: Factors relating to severity, hospital characteristics, and insurance type were associated with hospital admissions through the ED among pediatric patients with asthma. Compared to Medicaid patients, privately insured patients had a higher rate of hospitalization.

508. Drug Utilization Study in Neonates of a Public Hospital in Brazil: Off-label, Unlicensed, Potentially Harmful Drugs, and Harmful Excipients

Djanilson Barbosa Santos,[1] Alcidésio Sales de Souza Júnior,[2] Helena Lutéscia Luna Coelho.[3] *[1]Centro de Ciências da Saúde, Universidade Federal do Recôncavo da Bahiao, Feira de Santana, Bahia, Brazil; [2]Hospital Materno Infantil de Brasília, Brasilia, Brazil; [3]Doctoral Program in Development and Technological Innovation in Drug, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil.*

Background: Lack of scientific evidence is the main problem involved in using medicines among neonates, especially those in critical care. Neonates are exposed to a large number of drugs that are used off-label and in an unlicensed manner.

Objectives: The aim of this study was to describe the drug use profile of neonates hospitalized in a neonatal intensive care unit (NICU) at a public hospital in Brazil and the characteristics of these drugs: unlicensed, off-label, and potential risks.

Methods: This 6-month retrospective cohort study in a NICU, among neonate inpatients staying for over 24 hours, used prescription data from electronic medical records. Drug information in the package leaflets and literature were compared. Harmful potential of drugs and excipients was evaluated in accordance with the literature. Exposure to drugs and harmful excipients was expressed as the incidence rate (IR). The data were stored and analyzed in Excel for Windows (version 7) and in the Stata (version 12).

Results: One hundred and ninety-two neonates received a total of 3290 prescriptions, averaging 17.1 prescriptions/neonate (±17.9) and 8.8 drugs/neonate (±5.9). The mean hospital stay was 18.8 days (±18.1), totaling 3617 neonate-days. Numbers of prescriptions and drugs were higher among neonates with gestational age (GA) <31 weeks ($p < 0.05$). Anti-infectives and blood, digestive tract drugs, were the most frequent groups, with use varying according to GA. Immature neonates were more frequently exposed to unlicensed drugs (UL) and off-label use (OL) ($p < 0.05$). Most OL drugs had indications for newborns. Fifteen high-alert medications were used for >70% of the neonates. Of the neonates, 91.6% were exposed to harmful potential of drugs and excipients.

Conclusions: This study demonstrates that newborns are exposed to a large number of drugs and excipients potentially harmful, especially in relation to extremely preterm neonates. Neonates in a Brazilian NICU were exposed to a variety of OL, UL, and potentially

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harmful drugs and excipients, which is an alarming situation.

509. Performance of Signal Detection Algorithms in the Paediatric Dataset of the Publicly Available US FDA Adverse Event Reporting System (FAERS)

Osemeke Osokogu,[1] Caitlin Dodd,[1] Daniel Weibel,[1] Erik van Mulligen,[1] Florentia Kaguelidou,[1] Miriam Sturkenboom.[1] [1]*Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands.*

Background: Paediatric safety signal detection in spontaneous reporting databases requires appropriate methods due to confounding and potential effect modification by age.

Objectives: The aim of this study was to evaluate the performance of four signal detection algorithms on a predefined reference set of positive ($n=37$) and negative ($n=90$) controls that were specifically defined for the paediatric age group.

Methods: Data were obtained from the publicly available FAERS dataset spanning January 2004 to August 2012. All reports with missing age, age 0 (with a preferred term specific to antenatal exposure), and age >18 years were excluded, leaving only reports pertaining to age group 0–18 years. Performance was tested based on a recently published reference set (Drug Safety), which included 17 positive controls (PCs) that were assessed in the paediatric age group and 20 with evidence from adults. In total, we used 90 negative controls. All drugs and adverse events were mapped to 'World Health Organization-Anatomical Therapeutic Chemical' and 'Medical Dictionary for Regulatory Activities' codes, respectively. We evaluated the Urn-based reporting ratio (RR-urn), proportional reporting ratio (PRR), information component (IC) and empirical Bayes geometric mean (EBGM) against the reference set, by calculating 'area under the curve' (AUC).

Results: Altogether, 4 285 088 reports were retrieved out of which 4 169 414 (97.3%) were excluded: 34.0% (missing age), 0.1% (age 0, with antenatal-specific preferred terms), 65.8% (age >18 years) and 0.1% (duplicates). Finally, we analysed 115 674 reports. AUC values, based on 37 PCs (and separately 17 paediatric-specific PCs: values in brackets), were RR-urn 0.77 (0.83), PRR 0.77 (0.83), IC 0.77 (0.86) and EBGM 0.77 (0.84).

Conclusions: All the methods performed better when evaluated against paediatric-specific evidence; methods with shrinkage seem to perform best in this dataset, which may be explained by the often low numbers of cases in the paediatric age group.

510. Characterization of Patients with End-stage Heart Failure Secondary to Anthracycline Cardiac Toxicity

Garry R. Thomas,[1] Michael A. McDonald,[1,2] Heather J. Ross,[1,2] Diego H. Delgado,[1,2] Billia Filio,[1,2] Thavendiranathan Paaladinesh.[1,2] [1]*Department of Medicine, University of Toronto, Toronto, ON, Canada;* [2]*Division of Cardiology, Peter Munk Centre, University Health Network, Toronto, ON, Canada.*

Background: Anthracyclines (AC) are effective antineoplastic agents, remaining the cornerstone of therapy for many malignancies, but they are associated with cardiac toxicity. This can manifest as cardiomyopathy with an understudied subset of patients developing end-stage heart failure (HF) requiring ventricular assist device (VAD) or heart transplant (HT).

Objectives: We sought to describe the demographics, comorbidities and advanced therapeutic strategies adopted in patients with end-stage HF secondary to anthracycline-induced cardiomyopathy (AICM) managed at our centre.

Methods: This is a retrospective cohort study based at a large Canadian HF centre. Our database of patients who received VAD or HT for end-stage HF was reviewed ($N=421$), and those with AICM were identified ($N=17$, 4%). For comparison, patients with idiopathic non-ischemic cardiomyopathy (NICM) from the same database were matched at a 3:1 ratio for year and age of HF onset. Discrete variables were analyzed using a two-tailed Fisher exact test and continuous variables using the Mann–Whitney rank sum test. A p-value of <0.05 was considered significant.

Results: The clinical onset of HF occurred at 8.3 ± 8.9 years following AC exposure. AICM patients were predominantly female (70.6% vs 23.5%, $p=0.001$) and trended towards fewer comorbidities (hypertension, diabetes and dyslipidemia) than in NICM. A lower proportion of AICM patients had VADs implanted (47.1% vs 82.4%, $p=0.009$) with a trend towards older age at insertion (50.8 ± 11.7 years vs 41.5 ± 16.7 years, $p=0.08$). Almost all VADs were

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implanted with the strategy of 'bridge to transplant/candidacy'. No difference was observed between cohorts with respect to age, year or proportion receiving HT. To date, 21.4% of AICM patients developed a recurrence of their malignancy post-HT compared to 6.3% of NICM patients, with no history of cancer, who developed B cell lymphoma ($p = 0.13$).

Conclusions: Among patients receiving advanced HF management at a large Canadian HF centre, 4% of patients had AICM. AICM differed from a comparison cohort of NICM in terms of gender, comorbidities and likelihood of VAD insertion. Malignancy recurrence was common in AICM post-HT.

511. NIS/AHRQ-derived Epidemiologic Evidence on Modifying Effects of Sex and Race on Arthroplasty-related Outcomes

Yelizaveta Torosyan,[1] Tigran Karapetyan,[1] Nilsa Loyo-Berrios,[1] Danica Marinac-Dabic.[1] [1]*Division of Epidemiology, Center for Devices and Radiological Health, CDRH/FDA, Silver Spring, MD, USA.*

Background: Advanced medical device epidemiology that lays a background for implementation of precision medicine into clinical practice is a key prerequisite for enabling CDRH's vision to provide access to safe and effective devices.

Objectives: To enable more predictive evaluation of real-world performance of arthroplasty devices, we examined putative demographics-based modifying effects in the sex/race-stratified patient subpopulations with prostheses.

Methods: Nationwide Inpatient Sample (NIS) data from the Agency for Healthcare Research & Quality (AHRQ) were analyzed using the following ICD9 codes for main prosthesis-related diagnoses and procedures: V43.64, 81.51, 81.52, 81.53, 996.41, 996.42, 996.44, and 996.46. STATA was used for data management and analyses aimed to identify major sex/race-related trends in patients with prostheses including hip arthroplasty.

Results: The mechanical loosening (996.41) and articular bearing surface wear (996.46) of prosthetic joints in general occurred more frequently in female patients. However, race had an additional modifying effect, resulting in higher female/male ratios in Black versus White patients with these prosthesis-related adverse events. A more detailed analysis focused on hip arthroplasty (V43.64) suggested more intricate sex/race-related effects on the main adverse events such as wear, loosening, fracture, and dislocation. Although the hip arthroplasty-related adverse events mostly retained female predominance in both White and Black subpopulations, periprosthetic osteolysis (996.45) was more predominant in Black (but not in White) females compared to their male counterparts (chi-square $p < 0.006$).

Conclusions: Epidemiological evidence on these demographics-based trends points at the direct modifying effects of sex and race on prosthesis performance and implies the need for further research on possible—environmental and genetic—markers that could enable a more predictive analysis of prosthesis performance in patient subpopulations, thus facilitating precision medicine applications and enhancing safety of prosthetic devices.

512. Predictors of Early (6-month) Revision and All-cause Mortality Following Hip Arthroplasty: A Population-based Cohort Study

Albert Roso,[1] Cristian Tebé,[2,3] Mireia Espallargues,[2] Daniel Prieto-Alhambra,[1,4] PRESS-UP Study Investigators.[2] [1]*Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain;* [2]*Registre Catala d'Artroplasties (RACat), Agencia de Qualitat i Avaluacio Sanitaries de Catalunya, Generalitat de Catalunya, Barcelona, Catalonia, Spain;* [3]*Statistical Advisory Service, Bellvitge Biomedical Research Institute IDIBELL, Universitat de Barcelona, Barcelona, Catalonia, Spain;* [4]*Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, Oxfordshire, UK.*

Background: Hip arthroplasty (HA) is safe and cost effective. However, some patients might be at an increased risk of early revision or post-operative death.

Objectives: The aims of this study were to identify key predictors of 6-month post-HA revision and mortality and to derive prediction tools (PT) for both outcomes.

Methods: Data sources: primary care and hospital admission records linked to pharmacy dispensation data covering >80% of the Catalan population (www.sidiap.org) were linked to the Catalan Arthroplasty Registry.

Participants: patients undergoing HA in mid-2005/2012 for any reason except hip fracture or malignancy were included.

Study outcomes were all-cause revision and mortality in the 6-month post-HA.

Potential predictors were as follows: patient characteristics, lifestyle factors, GP visits previous year, drug utilisation, indication for HA, implant characteristics and centre volume.

Statistics: backwards stepwise logistic regression was used to identify key predictors of revision and mortality (two separate models). A PT was derived for each outcome based on the coefficients. Model discrimination and calibration were tested using AUC ROC and observed/expected plots. Multiple imputation was used to handle missing data.

Results: A total of 140/11 427 (1.2%) were revised, and 156/11 427 (1.4%) died in 6-month post-HA. Centre volume, body mass index, previous osteoporosis/fracture and NSAID use in the previous year were associated with both outcomes. Use of certain drugs (systemic steroids, anti-osteoporosis, proton pump inhibitors, anticonvulsants, tricyclic antidepressants and antibiotics) predicted revision, similarly age, sex, indication, Charlson index, smoking, drug use (anticoagulants, aromatase inhibitors and calcium/D supplements), number of GP visits and previous fracture related to mortality. Both PTs had good discrimination (AUC 71.0% for revision and 87.7% for death) and calibration.

Conclusions: HA surgery is cost beneficial for most patients, but a combination of patient and centre characteristics can help target individuals at risk of early revision or mortality. These PTs need external validation before they can be implemented.

513. National Trends and Cost Related to the Use of Minimally Invasive Device Technology in Urology

Bilal Chughtai,[1] Jialin Mao,[2] Abby Isaacs,[2] Richard Lee,[1] Alexis Te,[1] Steven Kaplan,[1] Peter Schlegel,[1] Art Sedrakyan.[2] *[1]Department of Urology, Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York City, NY, USA; [2]Department of Healthcare Policy and Research, Weill Medical College of Cornell University, New York City, NY, USA.*

Background: Introduction of minimally invasive surgery (MIS) and subsequent development of robotic techniques have a potential to dramatically shift practice patterns of major uro-oncology care.

Objectives: The aim of this study was to determine national trends in costs of care as well as associated growth of surgical caseload and adoption of MIS for major uro-oncology procedures.

Methods: In the nationally representative sample, we identified patients diagnosed with prostate, renal, and bladder cancer who underwent prostatectomy, nephrectomy, and cystectomy during 2000–2011. Temporal trends in patient demographics, hospital, and procedure-related characteristics, surgery volume, MIS utilization, and costs of hospitalization over years were analyzed. Hierarchical linear regression was performed to evaluate the effect of hospital volume, time, and surgery type on costs of hospitalization.

Results: Overall, 836 563, 440 337, and 122 992 patients underwent prostatectomy, nephrectomy, and cystectomy from 2000 to 2011. There was 33.6%, 50.8%, and 25.5% increase in annual surgery volume for these three surgeries over 10 years, with the most prominent increase in high-volume hospitals. The utilization of minimally invasive surgery increased 65.6% for prostatectomy, 22.0% for nephrectomy, and 12.5% for cystectomy. The increase was more prominent in high-volume hospitals. For all three surgeries, hospital stay for MIS patients was more expensive than that for open procedures but decreased during study period from $17 367 to $11 145 for prostatectomy and from $54 209 to $28 753 for cystectomy.

Conclusions: High-volume hospitals experienced higher growth in surgery caseloads and minimally invasive surgeries, but it did not lead to higher costs of care. While minimally invasive surgery has consistently been more expensive than open surgery, the costs for minimally invasive prostatectomy and cystectomy have decreased in the past decade.

514. National Trends in Utilization and In-hospital Outcomes of Mechanical versus Bioprosthetic Aortic Valve Replacements

Abby Isaacs,[1] Jeffrey Shuhaiber,[2] Arash Salemi,[3] O Wayne Isom,[3] Art Sedrakyan.[1] *[1]Department of Healthcare Policy and Research, Weill Cornell Medical College, New York City, NY, USA; [2]Department of Cardiothoracic Surgery, Rhode Island Hospital and Hasbro Children Hospital, Brown Medical School,*

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Providence, RI, USA; [3]Department of Cardiothoracic Surgery, New York Presbyterian Hospital–Weill Cornell Medical College, New York City, NY, USA.

Background: There is substantial controversy related to choice of a mechanical versus bioprosthetic prosthesis for aortic valve replacement (AVR) based on age criterion.

Objectives: This study aims to investigate national trends and in-hospital outcomes of the two prosthesis choices.

Methods: All patients aged greater than 18 in the National Inpatient Sample who received an AVR from 1998 to 2011 were considered. We examined utilization by patient, procedural, and hospital characteristics. We then used logistic regression to create a propensity score for the probability of receiving a bioprosthetic valve based on known confounders associated with patient outcomes and used nearest neighbor matching to create a balanced cohort. Balance was assessed using standard differences and the post-match *c*-statistic. Statistical significance was determined using chi-squared tests for categorical and Wilcoxon tests for continuous variables, with analogous paired versions used in the propensity-matched cohort.

Results: Bioprosthetic valves were 53.3% of 767 375 implanted valves, increasing in use from 37.7% in 1998–2001 to 63.6% in 2007–2011. Median age was 74 years for bioprosthetic valve patients and 67 years for mechanical. Utilization of bioprosthetic valves has increased across all age groups, most markedly in patients 55–64 years. Bioprosthetic valve patients had higher incidence of renal disease (8.0% vs 4.2%), coronary artery disease (58.5% vs 50.5%), and concomitant CABG (46.7% vs 41.9%) and have surgery in a high (>250 cases per year) volume center (31.3% vs 18.5%). Bioprosthetic valve patients had higher occurrence of in-hospital complications (55.9% vs 48.6%) but lower in-hospital mortality (4.4% vs 4.9%) than mechanical valve patients. This was confirmed in propensity-matched analyses (complications: 52.7% vs 51.5%; mortality: 4.3% vs 5.2%).

Conclusions: Utilization of bioprosthetic AVR has increased dramatically from 1998 to 2011. Prosthesis selection varies significantly by facility, with low-volume facilities favoring mechanical valves. Bioprosthetic AVR is associated with lower in-hospital mortality compared to mechanical.

515. Comparison of Open, Laparoscopic, and Robotic Colectomy in a National Database: Outcomes and Trends Related to Hospital Volume

Heather Yeo,[1,2] Abby Isaacs,[2] Jeffrey Milsom,[1] Art Sedrakyan.[2] *[1]Department of Surgery, New York Presbyterian Hospital–Weill Cornell Medical College, New York City, NY, USA; [2]Department of Healthcare Policy and Research, Weill Cornell Medical College, New York City, NY, USA.*

Background: Studies report that high-volume centers and use of laparoscopy can improve outcomes of surgery; however, current trends in colectomy and the rate and outcomes of robotic colectomy are unknown.

Objectives: This study aimed to examine trends in use of open (OC), robotic (RC), and laparoscopic (LC) colectomy and to compare outcomes of RC and LC.

Methods: Using the National Inpatient Sample, we evaluated all patients undergoing elective OC, LC, and RC from 2009 to 2012. Differences in patient and institutional characteristics between procedure groups are compared graphically using chi-squared tests. In-hospital outcomes are compared between groups using adjusted hierarchical logistic regression models, which account for the clustering of patients within hospitals. Cost is compared using non-parametric tests.

Results: A total of 509 029 patients underwent elective colectomy from 2009 to 2012. Of those, 266 263 (52.3%) were OC, 235 080 (46.2%) were LC, and 7686 (1.5%) were RC. The majority of LC and RC were performed at high-volume (37.5% of LC and 44.4% of RC) versus low-volume centers (28.0% of LC and 22.7% of RC). The percentage of RC increased nearly fivefold from 0.6% in 2009 to 2.8% in 2012, while LC use increased only slightly from 44% in 2009 to 48.2% in 2012. In high-volume facilities, there is an increase in case volume for both MIS and open procedures, but the increase is much larger for MIS surgeries. Overall, after adjusting for other factors, the rate of iatrogenic complications was significantly higher for RC than for LC; adjusted odds ratio 1.73 (1.20–2.47) and the median estimated costs of RC were higher $15 649 (IQR: 11 840–20 183) versus $12 071 (IQR: 9338–16 203), $p < 0.0001$, than of LC. The variation in in-hospital outcomes between RC, LC, and OC appears to be consistent across hospital volume groups.

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Conclusions: Our results show that the majority of colectomies are still being performed open despite data showing the benefits of LC. Use of RC has increased dramatically but still represents a small percentage of overall colectomies. RC is associated with higher costs and iatrogenic complications than LC.

516. Relationships between Total Hip Replacement Characteristics and Its Survivorship at Three Years in 100 191 Patients: A Population-based Study

Sandrine Colas,[1] Cédric Collin,[1] Philippe Piriou,[2] Mahmoud Zureik.[1] *[1]Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France; [2]Orthopedic Surgery, Raymond Poincaré Hospital, Garches, France.*

Background: Total hip replacement (THR) is efficient in treating hip arthritis. Results may be different according to implant characteristics: THR fixation technique and bearing surface could be related to prosthetic survivorship.

Objectives: This study aimed to compare THR survivorship according to cement type and according to bearing surface.

Methods: The cohort included all French patients aged 40 or over, who had undergone a THR between April 2010 and December 2011 for arthritis, using French health insurance databases. Patients were followed until December 2013. THR survivorship was assessed by THR cement type and bearing surface in univariate and multivariate Cox models, adjusted for patient and implanting center characteristics. Antibiotic-free cemented THRs and antibiotic-impregnated cemented THRs were compared to uncemented THRs. Ceramic on ceramic (CoC), ceramic on polyethylene (CoP) and metal on metal (MoM) THRs were compared to metal on polyethylene (MoP) THRs. The outcome was the revision of the implant.

Results: Study cohort comprised 100 191 subjects (baseline mean age 69.5 years, 56.6% women, 74.8% uncemented, 3.8% antibiotic-free cemented and 21.4% antibiotic-impregnated cemented THRs, 40.9% CoC, 33.9% MoP, 20.8% CoP and 4.4% MoM). During the median 33-month follow-up period, 3142 subjects underwent prosthetic revision. Antibiotic-impregnated cemented THRs had a better prognosis than uncemented THRs: cumulative revision rates were respectively 2.4% versus 3.3% ($p < 0.001$), and multivariate adjusted hazard ratio (aHR) was 0.75 (95%CI, 0.67–0.84; $p < 0.001$). This relationship was particularly marked in women. CoP and CoC THRs were no different from MoP. MoM had slightly shorter survivorship compared with MoP (aHR = 1.20; 95%CI, 1.01–1.43; $p < 0.001$).

Conclusions: THR characteristics are related to implant survivorship: antibiotic-impregnated cemented THRs have a better prognosis, and MoM THRs have a slightly worse prognosis. These findings are useful in helping surgeons select a THR fixation technique and helpful for the patient in the decision-making process with his surgeon.

517. How Risky Is Morcellation? Population-based Estimates of Prevalence of Uterine Sarcoma among Leiomyomata Patients Undergoing Surgical Treatment

Jialin Mao,[1] Samantha Pfeifer,[2] Xi E Zheng,[1] Peter Schlegel,[3] Art Sedrakyan.[1] *[1]Department of Healthcare Policy and Research, Weill Medical College of Cornell University, New York City, NY, USA; [2]Department of Obstetrics and Gynecology, Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York City, NY, USA; [3]Department of Urology, Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York City, NY, USA.*

Background: In April 2014, the US Food and Drug Administration discouraged the use of morcellation in managing uterine fibroid over concerns that it may spread unsuspected sarcoma tissue.

Objectives: This study aimed to estimate uterine sarcoma prevalence among patients having surgery for uterine fibroid and to determine risks of major complications following open surgery from population-level database.

Methods: We identified uterine sarcoma cases from all California registries of Surveillance, Epidemiology, and End Results data during 2008–2011. Population denominators were obtained by selecting patients undergoing hysterectomy or myomectomy from California State Inpatient and Ambulatory Surgery Database for the same years. We calculated two sets of estimates

to provide a reasonable range of uterine sarcoma prevalence. Estimate 1 was obtained by using population denominator of patients with leiomyomata diagnosis who had hysterectomy or myomectomy, which overestimates the prevalence of uterine sarcoma. Estimate 2 included all patients who underwent hysterectomy or myomectomy, regardless of their clinical diagnosis, leading to an underestimation of uterine sarcoma prevalence. Major complications following open surgery in California during 2008–2011 were examined.

Results: The sarcoma prevalence estimates were highly age dependent, lowest for women under age 50 (0.08–0.13%) and highest for women over 60 (0.36–1.53%). Race stratification showed a higher prevalence in White (0.25–0.51%) and Black (0.27–0.32%) women than those of other races (0.08–0.13%). Stratified by three age groups, open surgery was associated with 0.01% and 0.32% risks of in-hospital mortality and acute myocardial infarction (AMI) in women under 50 and 0.33% and 0.92% risks of mortality and AMI in women over 60.

Conclusions: We found more than 10-fold higher prevalence of uterine sarcoma among women over 60 compared to women under age 50. We also observed risks of death and lethal complications following open surgery for uterine leiomyoma. The risk of cancer dissemination should be weighed against possible reduced risks of complications following open surgery.

518. Effect of Femoral Head Size on the Rate of Revision Surgeries among Metal-on-metal Total Hip Replacements: A Propensity Score-matched Cohort Study from the Veterans Health Administration

Katherine Etter,[1,2] Art Sedrakyan,[3] Lee E. Rubin,[4] Linda Resnik,[1,2] Ira Wilson,[1] David D. Dore.[5,1] *[1]Health Services, Policy & Practice, Brown University, Providence, RI, USA; [2]Center for Restorative and Regenerative Medicine, Providence VA Medical Center, Providence, RI, USA; [3]Healthcare Policy and Research, Weill Cornell Medical College, New York City, NY, USA; [4]Department of Orthopaedics, Warren Alpert Medical School, Providence, RI, USA; [5]Optum Epidemiology, Waltham, MA, USA.*

Background: Metal-on-metal (MOM) total hip replacements hold the promise of lower wear rates and larger, more stable femoral head sizes. However, analyses using data from several large international registries show increased rates of surgical revision with these devices, although these registries lacked data on patient characteristics to adequately adjust for confounding.

Objectives: This study aimed to estimate the effect of femoral head size on the rate of revision surgery for MOM devices.

Methods: In this cohort study, we used administrative data from the Veterans Health Administration (VHA) on all veterans between 2002 and 2011 who underwent an initial hip replacement surgery and received a MOM device. Information on device surface materials and femoral head size came from linkage to the VHA's National Patient Prosthetic Database. We compared rates of revision surgery among recipients of a femoral head size >36 mm to recipients of ≤36 mm who were matched on high dimensional propensity scores. Hazard ratios came from proportional hazard regression models.

Results: Veterans in this cohort were predominately White (77%) and male (93.9%) with a mean age of 59.6 and a body mass index of 29.7. Three hundred and forty-nine veterans who received the smaller head size were matched to 349 veterans who had received the larger. The risk of revision for veterans who received a MOM implant with a head size >36 mm was 2.3 times (95%CI: 1.06, 5.41) the risk for those who received a smaller head size. By 8 years of follow-up, 8.8% of recipients of the >36 mm devices had revision surgery compared to 4.7% of recipients of ≤36 mm products.

Conclusions: Recipients of a MOM device with large femoral heads had more than double the rate of revision surgery.

519. Opioid Use as an Early Indication of Total Knee Arthroplasty Failure

Maria C. S. Inacio,[1,2] Robert S. Namba,[3] Nicole L. Pratt,[2] Stephen E. Graves,[4] Elizabeth E. Roughead,[2] Craig T. Cheetham,[5] Elizabeth W. Paxton.[1] *[1]Surgical Outcomes and Analysis, Kaiser Permanente, San Diego, CA, USA; [2]School of Pharmacy, University of South Australia, Adelaide, South Australia, Australia; [3]Orthopaedics, Southern California Permanente Medical Group, Kaiser Permanente, Irvine, CA, USA;*

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[4]*National Joint Replacement Registry, Australian Orthopaedic Association, Adelaide, South Australia, Australia;* [5]*Research & Evaluation, Southern California Permanente Medical Group, Kaiser Permanente, Pasadena, CA, USA.*

Background: A criticism of total knee arthroplasty (TKA) survivorship analysis is that the usual endpoint is revision surgery, which is a low-frequency complication that most often occurs late. TKA is undertaken to relieve pain, and persistent pain after surgery is a strong indication that the procedure was not successful. Few studies have evaluated whether post-operative narcotic analgesic use could be used as a surrogate for pain assessment and as a possible indicator for early failure.

Objectives: This study aimed to evaluate the association of opioid use and aseptic revision surgery after TKA.

Methods: A cohort study of primary TKAs registered in an integrated healthcare system's Total Joint Replacement Registry (01/08–12/11) was conducted. Adults with unilateral TKA for osteoarthritis were evaluated. Opioid use, the year after TKA, was the exposure of interest, and daily oral morphine equivalent (OME) amounts were calculated. Total post-TKA OMEs per 90-day exposure periods were categorized into quartiles. The endpoint was revision within 1 and 5 years. Survival analyses were conducted. Hazard ratios (HRs) were adjusted for patient age, gender, prior analgesic use, co-morbidities, and chronic pain diagnoses.

Results: Of the 24 105 patients, 62.7% ($N = 15\,112$) were females, median age was 68 years, and in the year prior to TKA, 59.7% ($N = 14\,401$) used opioids. After the rehabilitation period (days ≥91), at least 41.5% ($N = 9914$) continued to use opioids. One hundred fifty-five (0.6%) revisions occurred within 1 year and 377 (1.6%) within 5 years. Compared to patients not taking opioids, patients using medium-low to high total amounts of OMEs after rehabilitation had a higher adjusted risk of 1-year revision, ranging from HR = 2.4 (95% confidence interval (CI) 1.3–4.5) to HR = 33 (95%CI: 10–110), depending on the OME amount and time period. Use of opioids after rehabilitation was also associated with a higher risk of 5-year revision, ranging from HR = 2.0 (95%CI: 1.4–2.9) to 4.3 (95%CI: 2.8–6.6), depending on the OME amount and time period.

Conclusions: High and persistent use of opioids beyond the rehabilitation period is associated with 1-year and 5-year revision TKA surgery, and therefore, opioid use could be used as an indicator for early revision surgery.

520. Effect of Femoral Head Size in Non-metal-on-metal Devices on Surgical Revision Rates in Total Hip Replacements: A Propensity Score-matched Cohort from the Veterans Health Administration

Katherine Etter,[1,2] Art Sedrakyan,[3] Lee E. Rubin,[4] Linda Resnik,[1,2] Ira Wilson,[1] David D. Dore.[5,1]
[1]*Health Services, Policy & Practice, Brown University, Providence, RI, USA;* [2]*Center for Restorative and Regenerative Medicine, Providence VA Medical Center, Providence, RI, USA;* [3]*Healthcare Policy and Research, Weill Cornell Medical College, New York City, NY, USA;* [4]*Department of Orthopaedics, Warren Alpert Medical School, Providence, RI, USA;* [5]*Optum Epidemiology, Waltham, MA, USA.*

Background: With the development of thinner and stronger bearing surface materials, the femoral head sizes of total hip replacements have increased to prevent dislocation, improve stability, and increase range of motion. However, larger head sizes may have higher volumetric wear.

Objectives: This study aimed to estimate the effect of femoral head size on the rate of revision surgery for non-metal-on-metal total hip replacements.

Methods: In this cohort study, we used administrative data from the Veterans Health Administration (VHA) on all veterans between 2002 and 2011 who received a non-metal-on-metal total hip replacement. Information on device surface materials came from linkage to the VHA's National Patient Prosthetic Database. We compared rates of revision surgery among recipients of a small (<32 mm), medium (32 mm), and large (>32 mm) head sizes after matching on a high-dimensional propensity score. Hazard ratios came from proportional hazards regression models.

Results: Veterans in this cohort were predominately White (83.1%) and male (94.5%) with a mean age of 63.5 and a body mass index of 30. Seven hundred and seventy-nine recipients of a small femoral head and 1418 recipients of a large head were matched to recipients of a medium head. There was no apparent difference in the rate of revision surgery for medium-

head versus small-head devices (HR: 0.78, 95%CI: 0.48–1.26). Recipients of a large femoral head had a 34% increase in risk of revision relative to medium heads (HR: 1.34, 95%CI: 0.92–1.97).

Conclusions: Non-metal-on-metal devices with large femoral heads may increase the risk for revision surgery, although residual confounding related to patient anatomy cannot be ruled out.

521. Effect of Bearing Surface Material on Surgical Revision Rates in Total Hip Replacements: A Propensity Score-matched Cohort from the Veterans Health Administration

Katherine Etter,[1,2] Art Sedrakyan,[3] Lee E. Rubin,[4] Linda Resnik,[1,2] Ira Wilson,[1] David D. Dore.[5,1] *[1]Health Services, Policy & Practice, Brown University, Providence, RI, USA; [2]Center for Restorative and Regenerative Medicine, Providence VA Medical Center, Providence, RI, USA; [3]Healthcare Policy and Research, Weill Cornell Medical College, New York City, NY, USA; [4]Department of Orthopaedics, Warren Alpert Medical School, Providence, RI, USA; [5]Optum, Waltham, MA, USA.*

Background: Different classes of total hip replacement devices are constructed of different materials, and there is minimal evidence to guide the selection of a particular implant type even though total hip replacement is one of the most common major surgeries in the USA.

Objectives: The aim of this study was to estimate the effect of bearing surface materials on the rate of revision surgery for total hip replacements.

Methods: In this cohort study, we used administrative data from the Veterans Health Administration (VHA) on all veterans who received a total hip replacement between 2002 and 2011. Information on device surface materials came from linkage to the VHA's National Patient Prosthetic Database. We compared rates of revision surgery among recipients of alternative bearing surface (ceramic-on-ceramic (COC), ceramic-on-polyethylene (COP), and metal-on-metal (MOM)) devices to recipients of conventional metal-on-poly (MOP) devices who were matched in variable ratios on high-dimensional propensity scores. Hazard ratios came from proportional hazards regression models.

Results: Veterans were predominately White (83.1%) and male (94.5%) with a mean age of 63.5 and a body mass index of 30. One hundred and ninety-eight COC, 728 COP, and 569 MOM recipients matched to recipients of MOP devices. Relative to MOP, there were no statistically evident differences in the rate of revision surgery with COC (HR: 0.55, 95%CI: 0.22–1.2), COP (HR: 0.88, 95%CI: 0.52–1.45), or MOM (HR: 0.91, 95%CI: 0.52–1.52). At 8 years of follow-up, those with a COC had the lowest percentage of revision surgeries (5%) compared to MOP devices, which had the highest (11%).

Conclusions: We found no evident differences in the rate of surgical revision with different bearing surface materials. Our sample size was limited by VHA's low frequency of use of alternative bearing options.

522. Clipping and Coiling of Unruptured Intracranial Aneurysms (UIA) among Medicare Beneficiaries, 2000–2010

Jessica J. Jalbert,[1,2] Abby J. Isaacs,[1] Hooman Kamel,[1,3] Art Sedrakyan.[1] *[1]Department of Public Health, Weill Cornell Medical College, New York City, NY, USA; [2]LA-SER Analytica, New York City, NY, USA; [3]Department of Neurology and Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York City, NY, USA.*

Background: Endovascular coiling therapy is increasingly popular for obliteration of UIA. Older patients face a higher procedural risk and a shorter period during which rupture of an untreated UIA may cause subarachnoid hemorrhage (SAH). Trends in use and outcomes following UIA coiling and its alternative, surgical clipping, have not yet been investigated in the Medicare population.

Objectives: This study aimed to evaluate trends in the use of clipping and coiling for UIAs, trends in 30-day outcomes after clipping and coiling of UIAs, and trends in the occurrence of SAH among Medicare beneficiaries between 2000 and 2010.

Methods: Using 2000–2010 MEDPAR data, we identified Medicare patients ≥65 years of age continuously enrolled in Medicare ≥1 year prior to being admitted for clipping or coiling of a UIA. We calculated rates of clipping and coiling of UIAs per 100 000 Medicare beneficiaries as well as the rates of SAH in the entire Medicare population. We tested for trends over time in the risk of in-hospital mortality and complications, discharge destination,

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30-day mortality, 30-day readmissions, and length of hospitalization.

Results: Rates of procedural treatment of UIAs per 100 000 beneficiaries increased from 1.4 in 2000 to 6.0 in 2010, driven mainly by increased use of coiling. The characteristics and comorbidity burden of patients undergoing clipping (mean age: 70.6, 77.1% female, and mean Elixhauser comorbidity score: 3.4) or coiling (mean age: 72.5, 79.0% female, and mean Elixhauser comorbidity score: 2.4) did not change substantially over time; patients in later years were more likely to be treated by high-volume centers. Outcome risks decreased over time for both procedures, with 30-day mortality, in-hospital complications, and readmissions reaching lows in 2008–2010 of 1.6%, 25.0%, and 14.5% for clipping and 1.5%, 13.8%, and 11.0% for coiling, respectively. Rates of SAH did not decrease.

Conclusions: From 2000 to 2010, endovascular techniques were increasingly used to treat UIAs among Medicare beneficiaries. While outcomes tended to be more favorable over time, increased preventative UIA treatment did not result in a population-level decrease in SAH rates.

523. Extracorporeal Membrane Oxygenation (ECMO) Use among Children and Adults in the United States, 2009–2012

Sarah R. Hoffman,[1] Erika Avila Tang,[1] John C. Laschinger.[1] *[1]Center for Devices and Radiological Health (CDRH), US Food & Drug Administration, Silver Spring, MD, USA.*

Background: Extracorporeal membrane oxygenation (ECMO) provides life support to patients with severe heart and lung conditions. In recent years, ECMO use has increased for adult patients in the USA. In 2013, an FDA Advisory Panel recommended ECMO to be reclassified from classes III to II with special controls. Little is known about the distribution of reasons for ECMO use in the USA. Existing literature primarily focuses on adults or emphasizes national costs while leaving out information regarding the distribution and determinants of ECMO exposure and effectiveness.

Objectives: This study aimed to assess national utilization, including indications for use and mortality, of ECMO among adults and children in the USA.

Methods: Weighted national estimates for ECMO utilization, indications for use, and survival to discharge were obtained from the 2009–2012 Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) data. Results were stratified by age (adults: ≥18 years old; children: >17 years old) and by year. We used ICD-9-CM procedure code 39.65 to identify hospitalizations where ECMO was used.

Results: A slight increase in ECMO use was observed among children each year (2009: 1464, 2010: 1578, 2011: 1545, and 2012: 1785, p for trend = 0.12). The increase was higher among adults (2009, 1406, 2010: 1410, 2011: 1944, and 2012: 2725, p for trend = 0.07). The most common reasons for ECMO use were acute myocardial infarction for adults (~15%; unweighted mortality: 64%) and cardiac and circulatory congenital anomalies for children (~30%; unweighted mortality: 40%). Overall in-hospital mortality among pediatric ECMO patients remained ~40% throughout the 4-year period (p for trend = 0.13). Adult ECMO patients were less likely to survive to discharge; annual mortality for adult ECMO patients was 56.5% in 2009, 67.5% in 2010, 57.9% in 2011, and 59.3% in 2012 (p for trend = 0.04).

Conclusions: ECMO utilization among adults in the USA increased between 2009 and 2012, while pediatric utilization remained stable. Overall survival among adult ECMO users has decreased since 2009.

524. The Effect of Age on Re-intervention for Sling Implants in Stress Urinary Incontinence

Bilal Chughtai,[1] Jessica Buck,[1] Jialin Mao,[2] Richard Lee,[1] Alexis Te,[1] Steven Kaplan,[1] Art Sedrakyan.[2] *[1]Department of Urology, Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York City, NY, USA; [2]Department of Healthcare Policy and Research, Weill Medical College of Cornell University, New York City, NY, USA.*

Background: There has been no large population-based evidence for evaluation of sling failure in younger patients undergoing surgical intervention (SUI) for stress urinary incontinence.

Objectives: The aim of this study was to determine surgical outcomes after sling placement for stress urinary incontinence in various age groups.

Methods: Using the New York State Department of Health Statewide Planning and Research Cooperative System database, we identified female patients undergoing sling surgery between 2003 and 2011. Patients

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were divided into four groups according to their age at first sling procedure. Patient demographics, comorbidities, and hospital and surgeon volumes were examined. Unadjusted analysis for 90-day safety included urologic and non-urologic complications. General linear mixed model, accounting for clustering of patients under hospitals as random effect, was used to assess difference in treatment failure and urologic and non-urologic complications among age groups.

Results: We identified 35 134 patients undergoing sling procedures between 2003 and 2011, and 78.8% of them were younger than 65. When compared to younger age groups, older patients had higher risks of urinary tract infections (UTI), urinary retention as well as mechanical complications and non-urologic complications. At 1 year of follow-up, patients below the age of 50 were least likely to get a second intervention or revision (1.0%), and patients over 80 were most likely to experience treatment failure (2.8%). There was a decreasing trend of having a repeated sling procedure after failed initial sling procedure (<50 vs ≥80: 76.1% vs 50.0%). After adjusting for patient race, major comorbidities, and hospital and surgeon procedure, patients over 80 were more likely to experience urologic complications (OR, 1.69; 95%CI, 1.32–2.17) within 3 months following procedure and treatment failure (OR, 2.36; 95%CI, 1.49–3.76) within 1 year of follow-up, when compared to patients younger than 50.

Conclusions: There is a small but significant increase in non-urological complications and treatment failure for older patients. Older patients are less likely to receive slings than younger patients when being re-treated for SUI.

525. Spontaneous Reports for Toothbrushes: An Exemplar of Postmarket Vigilance for Low-risk Devices

Mary E. Ritchey,[1] Lisa Dunlap,[1] Kelly Solinsky,[1] Michael Steinbuch.[1] [1]*Global Safety Surveillance and Analysis, Procter & Gamble, Cincinnati, OH, USA.*

Background: In 2012, FDA issued a Consumer Update on "Spinbrush" toothbrush breakage and chipping/breaking teeth, and ISO published standards for manual (MTB) and powered toothbrushes (PB). Postmarket vigilance of these low-risk medical devices may identify/mitigate potential risks and provide learning for new products.

Objectives: We used toothbrushes as an exemplar of a multifaceted postmarket evaluation of low-risk devices.

Methods: We reviewed literature to identify adverse events (AE) and then analyzed AE in our spontaneous reporting system (SRS) and FDA manufacturer and user-facility device experience (MAUDE) data between July 2013 and June 2014. Outcomes were categorized using MedDRA in SRS and as injury, malfunction (mfn), and 'other' in MAUDE.

Results: The most common AE in literature were related to ingestion, impaction, and mouth-related trauma/injury. Device breakage and tooth chipping/breakage were not noted. SRS included 465 AE cases with 1163 PT for MTB and 1170 AE cases with 2725 PT for PB. MAUDE included 19 AE cases for MTB and 121 for PB across manufacturers.

Among MTB in MAUDE, there were four injury (21%) and 12 mfn cases (63%). For PB, there were 22 injury (18%) and 63 mfn cases (52%). One MTB (5%) and 30 PB (25%) were tooth chip/fracture. For PB reports, tooth chip/fracture ranged 19–81%, and device breakage ranged 24–85%. Excepting one manufacturer, combined device and tooth breakage were >80% of PB reports.

In SRS, the top PT potentially related to injury for MTB were gingival pain/bleeding/injury, oral pain, and toothache (28% of PTs). The top PT potentially related to injury for PB were lip/mouth injury, gingival pain/injury/bleeding, and oral/lip pain (34% of all PTs). Tooth fracture occurred in one MTB case and <2% of PB, and device breakage occurred in 11% MTB and 7% of PB cases.

Conclusions: This multifaceted monitoring approach enables a more proactive and thorough evaluation of these low-risk devices. Device and tooth breakage may occur but are rarely reported. Further work is warranted to understand key factors leading to more serious outcomes (e.g., device breakage, excluding bristles falling out) and underlying conditions, which predispose tooth chip/fracture.

526.A Quality-weighted Pooled Analysis of Single Proportions: A Case Study of Infections in Modular Endoprosthesis Implant

Grace Wangge,[1,2] Siti R. F. Saldi,[2] Meutia A. Kumaheri,[2] Yogi Prabowo,[3] Sudigdo Sastroasmoro,[2] Achmad F. Kamal.[3] [1]*Division of Epidemiology and Statistics, Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, DKI Jakarta, Indonesia;* [2]*Centre for Clinical Epidemiology and Evidence-based Medicine (CEEBM), Ciptomangunkusumo*

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Hospital/Faculty of Medicine, Universitas Indonesia, Jakarta, DKI Jakarta, Indonesia; [3]Orthopaedics and Traumatology, Ciptomangunkusumo Hospital/Faculty of Medicine, Universitas Indonesia, Jakarta, DKI Jakarta, Indonesia.

Background: Safety data on medical devices are often obtained solely from case series or reports. Thus, it is challenging to quantify the proportion of unexpected events of medical devices.

Objectives: This study aimed to assess the feasibility of integrates safety data from quality-weighted case series of medical devices.

Methods: We developed a quality-weighted-random-effect meta-analysis that integrates information from different data sources and gives preference to information from certain sources. As a case study, we applied the method in modular endoprosthesis implant and infection. A systematic search on major health technology assessment (HTA) databases, Cochrane, and Medline for case series was conducted. We included case series in limb salvage surgery involving knee joints among adult patients. Quality appraisal was performed using modified 20-criteria Delphi checklist from the Institute of Health Economics, Alberta, Canada, for individual studies.

Results: We included 10 case series published between 1997 and 2013 and reported 80 infection safety events from 640 patients with endoprosthesis. The rate of infections reported in the individual case series was ranged from 2% to 22%. Quality score of the publications was ranged from 9 to 14. Pooled infection proportions of all studies using our approach were 11.55% with 95% confidence interval (CI) 8.22–14.88%. The I-square was 95.7%. Including only studies with quality score of 14 resulted in pooled proportion of 12.19% (95%CI, 0.67–23.71%) and I-square of 96.5%.

Conclusions: Integrating safety data from quality-weighted case series of medical devices is feasible. The method gave a better precision of the pooled proportion rate, but further exploration is needed.

527. Increased Sensitivity and Negative Predictive Value with the Sysmex UF-1000i™ Urine Particle Analyzer Reduces the Need for Empirical Antibiotic Therapy

Meghan Riley,[1] Patrick Erdman,[1] Keri Donaldson.[1] *[1]Department of Pathology, Penn State Hershey Medical Center, Hershey, PA, USA.*

Background: Empiric antimicrobial use for a presumed urinary tract infection exposes patients to therapy for up to 48 hours prior to a negative culture result. We developed a new screening algorithm, using the Sysmex UF-1000i™ urine particle analyzer, which can increase diagnostic accuracy and decrease antibiotic exposure.

Objectives: This study aimed to develop a predictive urine screen and examine the cost effectiveness of this model in reducing antibiotic use.

Methods: Retrospective analysis-reviewed urine samples were collected over 3 months. Data were reviewed from traditional urine culture and urinalysis using the Sysmex UF-1000i™. Logistic regression was used to define what parameters were predictive of a positive culture: (1) trace bacteria, (2) trace yeast, and (3) WBC greater than 15 k/μL. Decreased days on therapy were then used to calculate reduced antimicrobial costs.

Results: A total of 4461 results were obtained (4088 from adult patients and 373 from pediatric patients). Among the adult patients, screen performance revealed a sensitivity of 98% (CI 97.4–98.4%), a specificity of 93.7% (CI 92.1–94.9%), and a negative predictive value (NPV) of 95.5% (CI 94.3–96.6%). Similar data were obtained for the pediatric population (269 true positives, 99 true negatives, 0 false positives, 5 false negatives, and an NPV of 95.1%). Given our annualized volume, this represents a reduction in 9990 urine culture tests per year, accounting for a savings of 19 980 patient days in saved exposure. Estimated antimicrobial material savings range from $11 088 to 889 000.

Conclusions: The automated urinalysis screen has a high NPV and will lead to a decrease in inappropriate antimicrobial use.

528. Accuracy of Optional ICD-9-CM Bearing Surface Codes for Total Hip Replacement in the Veterans Health Administration

Katherine Etter,[1,2] David D. Dore.[3,1] *[1]Health Services, Policy & Practice, Brown University, Providence, RI, USA; [2]Center for Restorative and Regenerative Medicine, Providence VA Medical Center, Providence, RI, USA; [3]Optum, Waltham, MA, USA.*

Background: Introduced in 2005, ICD-9 clinical modification codes for total hip replacement bearing surfaces have the potential to facilitate comparative effectiveness analysis in claims data; however, the accuracy of these codes in the USA is unknown.

Objectives: This study aimed to assess the accuracy of ICD-9 procedure modifier codes for total hip replacement bearing surface in the Veterans Health Administration (VHA).

Methods: We used data from the VHA's Corporate Data Warehouse to identify veterans with a total hip replacement surgery between October 2005 and 2011. These surgeries were matched to device order records in the National Patient Prosthetic Database (NPPD). The NPPD contains all transaction-level data and assigns ownership for surgical implants dispensed to veterans nationwide. Using the manufacturer's name and the model number from commercial device catalogs, we classified bearing surface materials for each NPPD listing. We estimated positive predictive values (PPV) of ICD-9 classifications relative to NPPD.

Results: ICD-9 bearing surface was coded for 2622 (35%) of surgeries for which we were able to assign bearing surface type from the NPPD order. NPPD data were missing for ICD-9 coded devices at the following rates: metal-on-polyethylene (MOP) 53%, metal-on-metal (MOM) 53%, ceramic-on-polyethylene (COP) 42%, and ceramic-on-ceramic (COC) 56%. The resulting cohort was predominately White (81%) and male (95%) with a mean age of 63 years. PPVs were highest for MOP (75%, 95%CI: 73–77%) and lower for MOM (64%, 95%CI: 61–68%), COP (70%, 95%CI: 66–75%), and COC devices (39%, 95%CI: 30–50%).

Conclusions: These data suggest that there is appreciable and varied misclassification of the ICD-9 codes across bearing surface types. Use of the ICD-9 modifiers for bearing surface in comparative effectiveness research should be done with caution. We were unable to identify bearing surface for all surgeries within the NPPD, thus limiting our sample size and, possibly, generalizability. Whether coding accuracy would vary greatly in a non-VHA system remains unaddressed.

529. Cardiovascular Risks Associated with Dipeptidyl-peptidase 4 Inhibitors: A Cohort Study

Maki Komamine,[1] Chieko Ishiguro,[1] Yoshiaki Uyama,[1] Emiko Kondo.[1] [1]*Office of Safety I, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan.*

Background: Some recent studies indicated that dipeptidyl-peptidase 4 (DPP–IV) inhibitors have no association with cardiovascular (CV) risks. However, there are few studies on the association between DPP–IV inhibitors and CV risks in Japanese patients.

Objectives: The aim of this study was to investigate the CV risks with DPP–IV inhibitors compared with other diabetes drugs by use of Japanese claims data.

Methods: Design: Using the Japan Medical Data Center claims database (2009–2013), we conducted a cohort study to compare CV risks associated with DPP–IV inhibitors and other diabetes drugs, which are known to have lower CV risks.

Setting: This study identified patients with a first prescription for any diabetes drugs.

Exposures: Exposure or control groups were defined as monotherapy users of DPP–IV inhibitors or BGs, respectively.

Main outcome measures: The CV events were defined as occurrence of cardiovascular diseases (CVDs) including acute myocardial infarction (AMI), cardiac failure, cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage coded by ICD–10.

Statistical analysis: We used standardized mortality ratio weighted (SMRW) analysis and Cox proportional hazard regression model to estimate the CV risks for DPP–IV inhibitors compared with BGs. Sensitivity analysis adjusting for propensity score (PS) was conducted.

Results: DPP–IV inhibitors and BGs were prescribed as a first-line drug to 3879 and 2129 patients, respectively. PS model included age, sex, and drugs and concomitant diseases. The use of DPP–IV inhibitors was not significantly associated with the occurrence of AMI relative to BGs (hazard ratio 0.92 [95%CI; 0.51, 1.67]). Similarly, no significant association with DPP–IV inhibitors was found in risks of other CVDs. The sensitivity analysis showed consistent result.

Conclusions: Monotherapy with DPP–IV inhibitors as a first-line drug has no association with increased risk of CVDs including AMI.

530. Domperidone, Cytochrome P450 3A4 Isoenzyme Inhibitors and Ventricular Arrhythmia: A Nationwide Case-crossover Study

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Hung-Lin Chen,[1] Pi-Hui Chao,[2] Jia-Jhen Chen,[2] Fei-Yuan Hsiao.[1,3,4] *[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Taiwan Drug Relief Foundation, Taipei, Taiwan; [3]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan; [4]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan.*

Background: Recent evidence has suggested that the oral form of domperidone may possess pro-arrhythmic effects and increase the risk of ventricular arrhythmia. The concomitant use of cytochrome P450 (CYP) 3A4 isoenzyme inhibitors may further potentiate this association. Nevertheless, empirical data supporting these associations are very limited.

Objectives: The aim of this study was to investigate the association between oral domperidone, CYP 3A4 inhibitors, and ventricular arrhythmia.

Methods: We identified 25 623 patients who were admitted or were seen in the emergency room for ventricular arrhythmia between 2000 and 2011 from Taiwan's National Health Insurance Research Database. We adopted a case-crossover study design to compare the exposure to oral domperidone for the same patient within a "case period" and within a "control period."

Results: Conditional logistic regression models showed that domperidone use was significantly associated with an increased risk of ventricular arrhythmia (aOR: 1.56; 95%CI [1.51–1.72]). The association was stronger with a higher daily dose of domperidone (>30 mg, aOR: 1.98 [1.50–2.63]). Furthermore, the concomitant use of domperidone and CYP 3A4 inhibitors was associated with an increased risk of ventricular arrhythmia (1 day: aOR 1.91 [1.33–2.75]; 3 days: aOR 1.90 [1.33–2.71]; and 7 days: aOR 1.80 [1.28–2.54]).

Conclusions: Our results suggested that oral domperidone was significantly associated with an increased risk of ventricular arrhythmia and that the association was stronger with exposure to >30 mg of domperidone. Furthermore, concomitant use of domperidone and CYP 3A4 inhibitors was associated with an increased risk of ventricular arrhythmia.

531. Systematic Review with Meta-analysis: The Association between the Use of Calcium Channel Blockers and Gastrointestinal Bleeding

Ying He,[1] Esther W. Chan,[1] Wai K. Leung,[2] Shweta Anand,[1] Ian C. K. Wong.[1] *[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong; [2]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong.*

Background: Due to their potential anti-platelet function, it is suggested that calcium channel blockers (CCBs) are associated with gastrointestinal bleeding (GIB). However, results from previous studies are conflicting.

Objectives: This study aimed to conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) and observational studies to clarify the association between CCBs and GIB.

Methods: We undertook a systematic search of PubMed, EMBASE, Cochrane library and Trial Register databases up to January 2015. Studies that evaluated exposure to CCBs reporting GIB outcomes with relative risks/odds ratios or provided data for their estimation were included in the meta-analysis. Random-effects models were used to calculate the pooled estimates.

Results: Seventeen studies (four RCTs, 11 case–control and two cohort studies) were included in the meta-analysis. The summary risk ratio (RR) for GIB was 1.17 (95%CI: 1.01–1.36) for CCB users versus nonusers. Exclusion of two studies that compared CCB with beta-blockers yielded a non-significant result (RR = 1.11, 95%CI: 0.95–1.26). Subgroup analysis showed that CCB users were 1.9-fold (95%CI: 1.44–2.62) more likely to develop GIB compared to beta-blocker users. CCB use was associated with a moderately higher risk of lower GIB (RR = 1.83, 95%CI: 1.17–2.84) but not upper GIB or peptic ulcer bleeding. An increased risk of GIB among CCB users was observed in studies that failed to adjust for use of anti-ulcer drugs or history of GIB.

Conclusions: Our meta-analysis suggests a marginal association between CCB use and the risk of GIB, which is of dubious clinical significance, as the effects of different comparators or adjustment for confounding factors renders this association non-significant. CCB use may be more associated with LGIB than UGIB/PUB. Based on the evidence from this meta-analysis, further studies are needed to investigate the potential protective effect on GIB of beta-blockers,

as well as the association between CCB use and risk of LGIB.

532. Metformin Exposure in Head and Neck Cancer Patients: Is There an Association with Improved Survival?

Matthew Alcusky,[1] Scott Keith,[2] Tom Karagiannis,[3] Carol Rabinowitz,[4] Daniel Louis,[4] Vittorio Maio.[1] *[1]School of Population Health, Thomas Jefferson University, Philadelphia, PA, USA; [2]Jefferson Medical College Department of Pharmacology and Experimental Therapeutics, Division of Biostatistics, Thomas Jefferson University, Philadelphia, PA, USA; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [4]Center for Research in Medical Education and Health Care, Thomas Jefferson University, Philadelphia, PA, USA.*

Background: Clinical studies of metformin in certain cancer types have demonstrated decreases in incidence and improvements in therapeutic response. Preclinical evidence supports multiple potential molecular pathways through which metformin may impart beneficial effects, which impede the development and growth of head and neck cancer (HNC).

Objectives: The aim of this study was to investigate the impact of metformin exposure following a diagnosis of HNC on the risk of all-cause mortality in a population-based cohort of Italian patients.

Methods: We used the Italian Emilia-Romagna Regional (RER) longitudinal healthcare database to conduct a retrospective cohort study following approximately 4 million adults (≥18) from 2003 to 2011. The RER database captures de-identified, fully linkable demographic, hospital discharge including ICD-9 diagnostic and procedure codes, outpatient pharmacy, and specialty data for all residents of the region. Resection status and metastases were used to stage the HNC patients based on surgical procedures and secondary malignancies. The primary outcome was adjusted risk of all-cause mortality in metformin-exposed HNC patients. Cox proportional hazard methods were used to model the covariate-adjusted time-dependent medication exposure survival association to minimize potential immortal time bias.

Results: During the study period, we identified 7872 patients diagnosed with HNC after which 708 (8.99%) were exposed at some point to metformin and 3626 (46.1%) died during follow-up (median = 2.98 years). Among them, after adjusting for potential confounders, we found no significant association between exposure to metformin and reduced risk of all-cause mortality (HR = 1.03, 95%CI: 0.84–1.26).

Conclusions: Our large population-based cohort study failed to find an advantage in survival outcomes for HNC cancer patients exposed to metformin, despite *in?vitro* mechanistic viability. Further research will be critical in clearly defining the role of metformin in HNC cancer survival through prospective studies and using similar modeling approaches.

533. The Role of Differential Work-up in the Association between Pioglitazone and Bladder Cancer

Elizabeth M. Garry,[1] John B. Buse,[2] Virginia Pate,[1] Til Stürmer.[1] *[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA.*

Background: A recent preliminary report from a 10-year study using commercial-based claims found no link between bladder cancer and pioglitazone (PIO) use, despite a safety warning issued by the Federal Drug Administration (FDA) in 2011. An explanation for inconsistent results regarding PIO safety throughout the published literature remains unclear.

Objectives: This study aimed to compare bladder cancer incidence and pre-diagnostic work-up for PIO versus dipeptidyl-peptidase-4 inhibitor (DPP-4) initiators in a nationally representative sample of elderly US patients, the population at greatest risk for bladder cancer.

Methods: A new-user active-comparator cohort study design that excluded prevalent cancer diagnoses was used to evaluate Medicare patients aged >65 with at least two new prescription claims within 180 days for one of the study drugs (PIO or DPP-4) between 2007 and 2012. Hazard ratios (HRs) and 95% confidence intervals (CIs) for bladder cancer were estimated using an as-treated approach with propensity score-adjusted Cox models. Similarly, proteinuria, hematuria, and edema diagnoses, as well as urinalysis, cytology, and cystoscopy procedure events, were evaluated independently of bladder cancer outcomes, to compare pre-diagnostic work-up between exposure groups.

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Results: Of the 48 228 patients who initiated PIO for a total of 71 570 person-years, 215 developed bladder cancer. Of the 54 632 patients who initiated DPP4 for a total of 69 861 person-years, 194 developed bladder cancer. The risk of bladder cancer for PIO was slightly higher than DPP therapy [HR(95% CI) = 1.03 (0.85,1.26)] in the age and sex-adjusted model with confidence limits inclusive of the null. The occurrence of edema was higher for PIO initiators [HR(95%CI) = 1.09 (1.06,1.12)], while the occurrence of the other pre-diagnostic events was lower.

Conclusions: Results suggest no increased bladder cancer risk associated with PIO therapy relative to DPP4. Further research is warranted to evaluate the potential for detection bias.

534. Thiazolidinediones and Parkinson's Disease: A Cohort Study

John G. Connolly,[1] Katsiaryna Bykov,[1] Joshua J. Gagne.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA.*

Background: Animal and epidemiologic studies suggest that nervous system inflammation may play a critical role in the development of Parkinson's disease. The diabetes drugs thiazolidinediones reduce inflammation and have shown a therapeutic benefit in animal models of Parkinson's disease.

Objectives: We examined the association between thiazolidinedione use and Parkinson's disease diagnosis in a cohort of older individuals.

Methods: We performed a cohort study of Medicare patients enrolled in state pharmaceutical benefits programs in Pennsylvania and New Jersey who initiated treatment with thiazolidinediones or sulfonylureas during the years 1997–2005 and had no prior diagnosis of Parkinson's disease. New users of thiazolidinediones were propensity score matched to sulfonylurea new users and followed for a first diagnosis of Parkinson's disease. After propensity score matching, we used Cox proportional hazards models to compare hazard ratios (HRs) of a Parkinson's disease diagnosis in users of thiazolidinediones compared to sulfonylureas. To assess the effect of duration of use, we performed several analyses requiring increasingly longer continuous medication use. All analyses were repeated in a secondary cohort without restrictions on prior diabetes drug use.

Results: Among 30 534 Medicare patients (5444 thiazolidinedione initiators and 25 090 sulfonylurea initiators) in the primary cohort, we observed 246 Parkinson's disease diagnoses during a mean follow-up of 2.95 years. The HR for Parkinson's disease diagnosis for thiazolidinedione users compared to sulfonylurea users was 1.08 (95% confidence interval [CI], 0.74–1.58). Increasing the duration of use requirements up to 10 months did not substantially change the association, with HRs ranging from 1.07 (95%CI, 0.57–2.00) to 1.31 (95%CI, 0.74–2.32). Results were similar in the secondary cohort.

Conclusions: Thiazolidinedione use was not associated with Parkinson's disease diagnosis compared to sulfonylurea use, regardless of increasing duration of exposure.

535. Comparative Risk of Acute Liver Injury Associated with Oral Azole Antifungal Drugs

Vincent Lo Re III,[1] Dena M. Carbonari,[1] James D. Lewis,[1] Kimberly A. Forde,[1] David S. Goldberg,[1] Rajender Reddy,[1] Kevin Haynes,[1] Jason Roy,[1] Daohang Sha,[1] Amy R. Marks,[2] Jennifer L. Schneider,[2] Brian L. Strom,[3] Douglas A. Corley.[2] *[1]Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [3]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; [4]Rutgers Biomedical & Health Sciences, Rutgers, the State University of New Jersey, Newark, NJ, USA.*

Background: Despite concerns regarding hepatotoxicity, limited information is available about the relative and absolute risks of acute liver injury associated with real-world use of oral azole antifungal medications. Further, it remains unclear if chronic liver disease increases rates of azole-associated acute liver injury.

Objectives: We evaluated the risk of acute liver injury associated with oral azole antifungal drugs and determined whether azole users with chronic liver disease had a higher risk of acute liver injury than users without pre-existing liver disease.

Methods: We conducted a cohort study among Kaiser Permanente Northern California members initiating an oral azole between 2004 and 2010. Outcomes included incident liver aminotransferases >200 μ/L (five times upper limit of normal) and severe acute liver injury (hepatic dysfunction, manifested by coagulopathy and hyperbilirubinemia). We calculated absolute risks and incidence rates of endpoints and evaluated the influence of chronic liver disease.

Results: Among 195 334 azole initiators (178 879 fluconazole; 14 296 ketoconazole; 1653 itraconazole; 478 voriconazole; and 28 posaconazole), absolute risks and rates (events/1000 person-years) of liver aminotransferases >200 μ/L were low with fluconazole (1/675 users; 13.0 [11.4–14.6]), ketoconazole (1/357; 19.3 [13.8–26.3]), and itraconazole (1/207; 24.5 [10.6–48.2]) but higher with voriconazole (1/23; 181.9 [112.6–278.0]) and posaconazole (1/14; 191.1 [23.1–690.4]). Severe acute liver injury was uncommon with fluconazole (1/4363; 2.0 [1.4–2.7]), ketoconazole (1/2383; 2.9 [1.1–6.3]), and itraconazole (0/1653; 0.0 [0.0–11.2]) but more frequent with voriconazole (1/239; 16.7 [2.0–60.2]) and posaconazole (1/28; 93.4 [2.4–520.6]). Chronic liver disease appeared to act as an effect modifier in associations between azoles and liver aminotransferases >200 μ/L (p for interaction, 0.08) but not for severe acute liver injury (p for interaction, 0.9).

Conclusions: Absolute risks and rates of acute liver injury were low for fluconazole, ketoconazole, and itraconazole. Chronic liver disease influenced the risk of severe liver aminotransferase elevations but not the risk of severe acute liver injury.

536. Fluoroquinolones Use and Development of Retinal Detachment: A Systematic Review and Meta-analysis

Carlos Alves,[1,2] Ana Penedones,[1,2] Diogo Mendes,[1,2] Francisco Batel Marques.[1,2] *[1]Central Portugal Regional Pharmacovigilance Unit (UFC), Centre for Health Technology Assessment and Drug Research (CHAD), AIBILI, Coimbra, Portugal; [2]School of Pharmacy, University of Coimbra, Coimbra, Portugal.*

Background: Lately, several pharmacoepidemiologic studies have been conducted evaluating the risk for retinal detachment associated with oral fluoroquinolones.

Objectives: This meta-analysis aims to investigate the association between fluoroquinolones and retinal detachment.

Methods: A literature search was conducted to identify relevant studies evaluating the risk for retinal detachment associated with oral fluoroquinolones. A meta-analysis was performed to pool rate ratios (RRs). Meta-regressions were conducted aiming to evaluate the influence of time interval between fluoroquinolones use and retinal detachment diagnosis or treatment one risk estimates.

Results: Seven observational studies were included. Overall, fluoroquinolones were associated with a slightly increased risk for retinal detachment [RR 1.09 (95%CI: 1.01–1.17); $p=0.03$; $I^2=42.0\%$]. However, when the analysis was stratified according to different study designs, the result was no longer statistically significant, with the exception of an increased risk identified for past users of fluoroquinolones, based on data from case–control studies [RR 1.07 (95%CI: 1.01–1.12); $p=0.01$; $I^2=0.0\%$]. According to meta-regressions, the risk for retinal detachment did not vary due to different time intervals between fluoroquinolones prescription and retinal detachment diagnosis or treatment.

Conclusions: There is limited evidence linking retinal detachment to oral fluoroquinolones. Upon the reevaluation of the benefit/risk ratio of fluoroquinolones, both FDA and Health Canada decided that no action was necessary, while EMA recommended updating the 'Warnings' section of fluoroquinolones' labels. If existing, an increase in the risk would be verified for individuals with a high baseline risk for developing retinal detachment.

537. Use of Fluoroquinolones Is Associated with Increased Risk for Nontraumatic Spontaneous Pneumothorax—A Population-based Study in a National Representative Cohort

Chien-Chang Lee,[1] Meng-tse Gabriel Lee,[2] Tse-Chih Chou,[3] Yi-Hsien Lin,[2] Shyr-Chyr Chen.[2] *[1]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou, Taiwan; [2]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]Chang Gung University, Taoyuan, Taiwan.*

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Background: Fluoroquinolones, which are broadly used antibacterial agents, have been associated with lesions in collagen. Lesions in the lung collagen may lead to nontraumatic spontaneous pneumothorax (NSP).

Objectives: This study aimed to evaluate the association between use of fluoroquinolones and NSP in a national representative cohort.

Methods: We conducted a population-based case–control study nested in the National Health Insurance Research Database of Taiwan between January 2000 and December 2011. Using risk-set sampling scheme, 100 controls were selected for each case matched on age and gender. We defined cases as the first primary diagnosis of NSP along with tube thoracotomy. We classified users of fluoroquinolones as current and past users, dependent on the exposure to fluoroquinolones within 3 months of index date. Conditional logistic regression analysis was used to adjust for various unbalanced covariates between users and non-users of fluoroquinolones.

Results: From a cohort of 1 million patients, 121 cases of NSP were identified. Current use of fluoroquinolones was associated with increased risk for developing NSP (crude rate ratio [RR], 4.14[95%CI, 0.56–30.91]), while past use showed an attenuated effect (RR, 2.9[95%CI, 0.7–11.99]). The increased risk for developing NSP remained for current (adjusted [RR], 4.98[95%CI, 0.66–37.56]) and past use ([ARR], 2.88[95%CI, 0.69–12.04]), after 70 individual covariate adjustments.

Conclusions: We found a non-negligible association between use of fluoroquinolones and development of NSPs. Further studies are needed to validate our findings. Physicians should be alert of the potential association when selecting antimicrobials for patients at high risk for NSP.

538. Rates of Anaphylaxis with Moxifloxacin: Verification of Case Status

Najat J. Ziyadeh,[1] Kiliana Suzart-Woischnik,[2] Frank Kruesmann,[3] Pierre Arvis,[4] N Franklin Adkinson, Jr,[5] Werner J. Pichler,[6] Gillian M. Shepherd,[7] John D. Seeger.[1,8] *[1]Epidemiology, Optum, Waltham, MA, USA; [2]HealthCare, Bayer, Berlin, Germany; [3]HealthCare, Bayer, Wuppertal, Germany; [4]HealthCare, Bayer, Loos, France; [5]Division of Allergy and Clinical Immunology, The Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA; [6]GmbH, ADR–AC, Bern, Switzerland; [7]Weill Medical College, Cornell University, New York City, NY, USA; [8]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA.*

Background: Fluoroquinolones have been associated with rare serious adverse effects including allergic reactions. Prior investigations of serious allergic reactions with fluoroquinolones are largely based on spontaneous reports lacking standardized outcome criteria and arising from uncertain source populations.

Objectives: We sought to validate potential cases of anaphylaxis identified following receipt of selected antibiotics within clearly defined populations and to compare incidence rates between moxifloxacin and other antibiotics (including β-lactams, macrolides, and fluoroquinolones). This study builds on a previous cohort study conducted within health insurance data by adding a second data source (clinical trials),expanding the anaphylaxis definition (more claims codes) and applying the same refined validation process (multiple clinical reviews applying the same operational definition of anaphylaxis) to cases from both data sources.

Methods: Data for this study arose from two sources: health insurance claims (between July 2000 and June 2004 within the Optum Research Database) and clinical trials (phases II–IV clinical trials through December 2008). Medical records or adverse event report(s) of potential anaphylaxis were reviewed and adjudicated by clinical experts using standardized criteria. Drug-specific incidence rates or odds ratios (moxifloxacin versus comparator antibiotics) were calculated using confirmed cases.

Results: Confirmed anaphylaxis (11.7% of potential cases) within the health insurance data occurred at a rate of 0.28 per 10 000 dispensings for moxifloxacin (95%CI: 0.12–0.54) and did not differ substantially across the drug groups. Confirmed cases of anaphylaxis (2.4% of potential cases) among the clinical trial data produced a pooled OR of 1.00 (95%CI: 0.34–2.91) for oral moxifloxacin relative to the comparator antibiotics. In the clinical trials using sequential (intravenous followed by oral) moxifloxacin, a pooled OR estimate of 1.00 (95%CI: 0.17–5.98) was observed.

Conclusions: Rates of anaphylaxis were similar across the antibiotics in this study. The small fraction of confirmed anaphylaxis supports the value of medical record validation and term mapping to remove false positives.

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539. Clinical Outcomes among Patients Who Are Prescribed Antibiotics with versus without Point-of-care Testing for Infection: A Danish Nationwide Population-based Cohort Study

Mette Søgaard,[1] Johnny Kahlert,[1] Reimar W. Thomsen,[1] Flemming Bro,[2] Henrik T. Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of General Practice, Department of Public Health, Aarhus University, Aarhus, Denmark.*

Background: Use of point-of-care (POC) tests such as C-reactive protein measurements, throat swabs, bacteriological cultures, and urinary tests may reduce diagnostic uncertainty and guide antibiotic treatment decisions. While studies have shown that POC testing may reduce antibiotic prescribing, there are little data on clinical outcomes associated with POC testing.

Objectives: The aim of this study was to examine the association between use of POC testing in general practice and risk of antibiotic shift, new GP consultation, hospitalization, and death among patients treated with antibiotics.

Methods: We used population-based healthcare registries to identify a random sample of 2 293 014 individuals treated with antibiotics from 2006 to 2012 and identified whether they were POC tested within 2 days prior to a redeemed prescription. We used Poisson regression with a robust error variance to compute the relative risk (RR) with 95% confidence intervals (CIs) of a new GP consultation or antibiotic prescription within 7 days, hospitalization within 7 days, and 30-day mortality, controlling for age, sex, comorbidity, and marital status.

Results: Among 2 293 014 individuals (median age of 38 years), 1 019 882 (44.5%) underwent POC testing prior to their antibiotic prescription. The risk of a new GP consultation within 7 days was 18.7% in individuals with POC testing and 15.0% in those without, resulting in an adjusted RR (aRR) of 1.22 (95%CI: 1.22–1.23). Similarly, we found increased risks of new antibiotic prescriptions (*aRR* = 1.41, 95%CI: 1.39–1.43), hospitalizations within 7 days (*aRR* = 1.29, 95% CI: 1.22–1.37), and 30-day mortality (*aRR* = 1.38, 95% CI: 1.31–1.46) among POC-tested individuals compared with individuals without prior POC testing.

Conclusions: In general practice, POC testing prior to prescription of antibiotics was associated with increased risk of new antibiotic prescriptions, new GP consultations, hospitalization, and death, indicating that individuals prescribed with antibiotics after POC testing are more likely to have severe infection than those without POC testing.

540. The Safety of Pegylated Interferon α-2a and α-2b Combined with Ribavirin in Patients with Chronic Hepatitis C Based on the Japanese Interferon Database

Izumi Sato,[1] Yohei Kawasaki,[2] Takumi Imai,[1] Sachiko Tanaka,[1] Hiroshi Yamada,[3] Koji Kawakami,[1] Naohiko Masaki.[4] *[1]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; [2]Faculty of Science, Tokyo University of Science, Tokyo, Japan; [3]Department of Drug Evaluation and Informatics, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan; [4]The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Chiba, Japan.*

Background: No studies have examined the safety of pegylated interferons (PEG-IFN), α-2a and α-2b, at the national level in Japan.

Objectives: Using the Japanese Interferon Database, the time to withdrawal from the two types of PEG-IFNs due to side effects was compared, and the factors influencing side effects were examined, considering regional differences.

Methods: A retrospective cohort study was performed using the Japanese Interferon Database. The data were collected by 36 local governments across Japan. This study included chronic hepatitis C patients with genotype 1 who received a combination therapy of PEG-IFN α-2a or α-2b with ribavirin in the database between December 2009 and April 2013. The difference between the two groups in the time to withdrawal from IFN therapy due to side effects was compared using the log-rank test. The hazard ratio between the two groups was obtained using an adjusted Cox regression analysis. A frailty model was used to consider the heterogeneity among local regions.

Results: A total of 8278 patients (α-2a, 2811 patients; α-2b, 5467 patients) were included in the study cohort. The numbers of patients who withdrew treatment due to side effects were 308 patients (10.95%) and 638 patients (11.67%) in the α-2a group and α-2b group, respectively. The most common adverse events were

malaise (α-2a, 142 patients [5.05%]; α-2b, 285 patients [5.21%]), followed by anorexia (86 [3.06%]; 176 [3.22%]) and psychoneurosis (63 [2.24%]; 135 [2.47%]). The groups did not differ in the time to withdrawal from treatment due to side effects ($p = 0.273$). The hazard ratio for withdrawal time in the Cox regression analysis was 0.914 (95% confidence interval 0.794–1.051; $p = 0.207$). The factors that influenced side effects were age (hazard ratio 1.043; $p < 0.0001$) and treatment experience (0.831; $p = 0.016$); the other factors had no influence. There was no difference between groups by using a frailty model (0.903; $p = 0.162$).

Conclusions: There was no difference in withdrawal time between PEG-IFN α-2a and α-2b, and these therapies were equally safe even after regional differences were taken into consideration.

541. Androgen Deprivation Therapy Use and the Risk of Venous Thromboembolism

Adi J. Klil-Drori,[1,2] Hui Yin,[1] Vicky Tagalakis,[1] Armen Aprikian,[3,4] Laurent Azoulay.[1,4] *[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [3]Department of Oncology, McGill University Hospital Centre, Montreal, QC, Canada; [4]Department of Oncology, McGill University, Montreal, QC, Canada.*

Background: The use of androgen deprivation therapy (ADT) has been associated with an increased risk of venous thromboembolism (VTE) in patients with prostate cancer, but data remain limited.

Objectives: This study aimed to determine whether the use of ADT in men with prostate cancer is associated with an increased incidence of VTE and to assess whether VTE risk varies by ADT type.

Methods: A population-based cohort of men over 40 years of age, newly diagnosed with prostate cancer between 1 April 1998 and 31 March 2014, was identified from the UK Clinical Practice Research Datalink linked to the Hospital Episode Statistics database. Men with a previous VTE, myeloproliferative neoplasm, and nephrotic syndrome were excluded. ADT composed of gonadotropin-releasing hormone (GnRH) agonists, oral antiandrogens (OAA), estrogens, and bilateral orchiectomy. The primary outcome was first hospitalized VTE, and the secondary outcome was hospitalized VTE associated with current ADT use stratified by ADT type. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for VTE associated with current and past use of ADT.

Results: A total of 21 729 men were included in the cohort. During a mean follow-up of 4.1 years, there were a total of 609 hospitalized incident VTEs. Compared with non-use, current ADT use was associated with a twofold increased risk of VTE (crude incidence rates: 10.1 vs 4.8 per 1000 person-years; HR: 1.99; 95%CI: 1.62–2.43), while there was no association with past use (HR: 1.09, 95%CI: 0.83–1.45). In the secondary analysis, current use of estrogens was associated with the highest risk (HR: 8.73, 95%CI: 4.06–18.79), followed by GnRH agonists and OAA combined (HR: 2.96, 95%CI: 2.21–3.97), bilateral orchiectomy (HR: 1.68, 95%CI: 0.69–4.11), GnRH agonists alone (HR: 1.61, 95%CI: 1.28–2.01), and OAA alone (HR: 1.48, 95%CI: 1.01–2.16).

Conclusions: Current use of ADT was associated with a twofold increased risk of VTE. The risk was elevated with all ADT types, including GnRH agonists.

542. Androgen Deprivation Therapy and the Incidence of Autoimmune Diseases in Patients with Prostate Cancer

Adi J. Klil-Drori,[1,2] Koray Tascilar,[1] Hui Yin,[1] Armen Aprikian,[3,4] Laurent Azoulay.[1,4] *[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [3]Department of Oncology, McGill University Hospital Centre, Montreal, QC, Canada; [4]Department of Oncology, McGill University, Montreal, QC, Canada.*

Background: The importance of androgen deprivation therapy (ADT) for the treatment of advanced prostate cancer has been recognized for more than seven decades. However, given that androgens regulate the immune system, little is known on the effect of ADT use on the incidence of autoimmune diseases.

Objectives: The aim of this study was to determine whether the use of ADT is associated with a change

in the incidence of inflammatory bowel disease (IBD), psoriasis/psoriatic arthritis (psoriasis), and rheumatoid arthritis (RA), separately.

Methods: A population-based cohort of men over 40 years of age, newly diagnosed with prostate cancer between 1 January 1988 and 30 September 2014, was identified from the UK Clinical Practice Research Datalink. Men with previous IBD, psoriasis/psoriatic arthritis (psoriasis), and rheumatoid arthritis (RA) were excluded. ADT composed of gonadotropin-releasing hormone agonists, oral antiandrogens, estrogens, and bilateral orchiectomy. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HR) with 95%CI IBD, psoriasis, and RA associated with current and past use of ADT. Separate analyses were conducted for each outcome.

Results: A total of 36 052 men were included in the main cohort. During a mean follow-up of 4.5 years (SD: 3.6), there were 79, 263, and 130 incident cases of IBD, psoriasis, and RA, respectively. Compared to no use, current use of ADT was associated with a 44% decreased risk of IBD (crude incidence rates: 0.7 and 0.4 per 1000 person-years [PY], adjusted HR: 0.56, 95%CI: 0.32–0.98). Current use of ADT was not associated with the incidence of psoriasis (crude incidence rates: 1.6 and 1.5 per 1000 PY; HR: 1.02, 95%CI: 0.75–1.38) and RA (crude incidence rates: 0.9 and 0.7 per 1000 PY; HR: 0.93, 95%CI: 0.61–1.43). Past use of ADT was not associated with the incidence of any of these conditions.

Conclusions: Current use of ADT in men with prostate cancer may decrease the risk of IBD. The clinical significance of androgens and androgen deprivation in autoimmunity in general, and gut inflammation specifically, warrants further investigation.

543. Effectiveness and Safety of Cetuximab as First-line Treatment in the Elderly with Metastatic Colorectal Cancer from the EREBUS Cohort

Annie Fourrier-Réglat,[1,2] Pernelle Noize,[2] Magali Rouyer,[1] Denis Smith,[3] Eric François,[4] Alain Monnereau,[5] Aurélie Balestra,[1] Jérémy Jové,[1] Régis Lassalle,[1] Nicholas Moore.[1,2] *[1]Pharmacology, University of Bordeaux, Bordeaux, France; [2]Pharmacology, CHU de Bordeaux, Bordeaux, France; [3]Oncology, CHU de Bordeaux, Bordeaux, France; [4]Oncology, Centre Lacassagne, Nice, France; [5]Clinical Research and Medical Information, Institut Bergonié, Bordeaux, France.*

Background: In view of the aging population, oncogeriatrics has become a priority for public health. Elderly cancer patients are often excluded from clinical trials, and there are no data from cohort studies regarding cetuximab use in such patients.

Objectives: As part of the EREBUS cohort, we aimed to compare cetuximab use, safety, and effectiveness in real-life practice between subjects aged >70 years (elderly) and ≤70 years (younger).

Methods: EREBUS is a French multicenter ($n=92$) cohort of 389 patients initiating cetuximab first-line therapy for unresectable metastatic colorectal cancer (mCRC) in 2009 or 2010 who were identified from hospital pharmacy dispensations and followed 24 months. As part of the EREBUS cohort, subjects >70 years versus those ≤70 years were compared according to cetuximab use, safety, and effectiveness in terms of progression-free survival (PFS) and tumor response rate.

Results: In the EREBUS cohort, 116 (29.8%) subjects were aged >70 years and 273 (70.2%) ≤70 years. As compared to the younger patients, the elderly were comparable in terms of gender (male: 62.1% vs 69.6%, $p=0.15$) and ECOG scores 0–1 (72.4% vs 80.2%, $p=0.12$). Median duration of cetuximab treatment was significantly shorter in the elderly (3.7 vs 5.3 months, $p=0.03$). Incidence of hematological (91.4% vs 90.8%, $p=0.87$), digestive (79.3% vs 85.7%, $p=0.12$), dermatological (77.6% vs 85.0%, $p=0.08$), and neurosensitive adverse events (37.9% vs 47.6%, $p=0.08$) was not statistically different. Effectiveness was not different between elderly and younger patients: median PFS, 9.5 months (95%CI [7.1–10.5]) versus 9.2 [8.1–9.8], and best overall tumor response rate, 46.5% (95%CI [37.4–55.6]) versus 56.7% [50.8–62.6].

Conclusions: In the EREBUS cohort, effectiveness and safety of cetuximab plus chemotherapy in elderly patients were not different to those observed for younger subjects, and similar outcomes have been reported for another targeted therapy for mCRC, bevacizumab in the ETNA cohort in France and in the BRITE cohort in the USA.

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544. Risk of Venous Thromboembolism in Cancer Patients Treated with Epoetins or Blood Transfusions

Antonios Douros,[1,2] Kathrin Jobski,[1] Bianca Kollhorst,[3] Tania Schink,[1] Edeltraut Garbe.[1] *[1]Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology—BIPS GmbH, Bremen, Germany; [2]Clinical Pharmacology and Toxicology, Charité—Universitätsmedizin Berlin, Berlin, Germany; [3]Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology—BIPS GmbH, Bremen, Germany.*

Background: Anemia is a common problem in patients with cancer, and its treatment includes blood transfusions or recombinant human erythropoietins, epoetins. Although epoetins have been associated with an increased risk of venous thromboembolism (VTE), studies comparing the VTE risk of both treatments in cancer patients have not been published so far.

Objectives: The aim of this study was to compare the risk of VTE in cancer patients receiving epoetins, blood transfusions, or both.

Methods: Our study is based on data from the German Pharmacoepidemiological Research Database (GePaRD) from 2004 to 2009. A nested case–control design was used to assess VTE risk in a cohort of incident cancer patients receiving epoetins, transfusions, or both. VTE was defined as a diagnosis of deep vein thrombosis of the leg/hip or pulmonary embolism. To each case, up to 10 controls were matched by year of birth, sex, and statutory health insurance provider. Past users of epoetins or transfusions served as reference group for all treatment groups. A binary logistic regression model was used to estimate confounder adjusted odds ratios (aORs) with 95% confidence intervals (CIs). It was adjusted for comorbidities including VTE risk factors, previous chemotherapy or surgery, drugs with thrombotic risk, antithrombotic medication, and metastatic disease.

Results: We identified 69 888 patients receiving a first-time treatment with epoetin or transfusion (median age at cohort entry 69 years, 53% women). During the time in cohort, 3316 patients were diagnosed with VTE (median age of 69 years, 60% women) and matched to 32 617 controls. The aOR for VTE was 1.31 (CI: 1.03–1.65) for epoetins, 2.33 (CI: 2.03–2.66) for transfusions, and 2.24 (CI: 1.34–3.77) for epoetins and transfusions. Sensitivity analyses with a more restrictive VTE definition or an expanded time window (90 instead of 28 days) yielded similar results. History of VTE was identified as a major risk factor for VTE (aOR: 14.76; CI: 12.79–17.03), followed by previous surgery (OR: 1.83; CI: 1.67–2.01), previous chemotherapy (OR: 1.65; CI: 1.50–1.82), and obesity (OR: 1.53; CI: 1.39–1.69).

Conclusions: Transfusions are associated with a higher VTE risk than epoetins in cancer patients.

545. Safety of Low Molecular Weight Heparin Compared to Unfractionated Heparin in Hemodialysis: A Systematic Review and Meta-analysis

Hind Harrak,[1] Émilie René,[1] Naoual Elftouh,[1] Jean-Philippe Lafrance.[1,2,3] *[1]Maisonneuve-Rosemont Hospital Research Center, Montreal, QC, Canada; [2]Department of Medicine, Université de Montréal, Montreal, QC, Canada; [3]Division of Nephrology, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada.*

Background: Low molecular weight heparins (LMWH) have been extensively studied and became the treatment of choice for several indications including pulmonary embolism. While their efficacy in hemodialysis is considered similar to unfractionated heparin (UFH), their safety remains controversial mainly due to a risk of accumulation in patients with renal impairment.

Objectives: The aim of this systematic review was to evaluate the safety of LMWH compared to UFH for extracorporeal circuit anticoagulation.

Methods: We used PUBMED, EMBASE, CENTRAL, TRIP and NICE to retrieve relevant studies with no language restriction. Reference lists were also screened manually. We searched for controlled experimental trials comparing LMWH to UFH for extracorporeal circuit anticoagulation among ESRD patients undergoing chronic hemodialysis. Studies were kept if they reported at least one of the following outcomes: bleeding events, lipid profile, cardiovascular events, osteoporosis or HIT. Two independent reviewers conducted studies' selection, quality assessment and data extraction with discrepancies solved by a third reviewer. Relative risk and 95%CI were calculated for dichotomous outcomes, and mean weighted difference (MWD) with 95%CI was used to pool continuous

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variables, with the DerSimonian and Laird method and the random effect model for heterogeneous data.

Results: Seventeen studies were selected as part of the systematic review from which nine reported bleeding events and 11 provided lipid profiles. The relative risk for total bleeding was 0.76 (95%CI: 0.26–2.22) with 60.8% heterogeneity. The MWD calculated for total cholesterol was −28.7 mg/dl (95%CI: −51.4 to −6.0), a MWD for triglycerides of −55.6 mg/dl (95%CI: −94.5 to −16.7) was estimated and finally, LDL cholesterol had a MWD of −14.9 mg/dl (95% CI: −36.3 to 6.5) with heterogeneity estimated at 87.8%, 85.8% and 88.3%, respectively.

Conclusions: LMWH showed to be at least as safe as UFH in chronic hemodialysis. The limited number of studies reporting on osteoporosis and HIT does not allow any conclusion for these outcomes. Larger studies are needed to evaluate properly the safety of LMWH in chronic hemodialysis.

546. Drug-associated Angioedema: Effect Modification by Race

Marsha E. Reichman,[1] Michael Wernecke,[2] John Yap,[1] Yoganand Chillarige,[2] Jiemin Liao,[2] Stephine Keeton,[1] Margie Goulding,[1] Katrina Mott,[1] Jeffrey A. Kelman,[3] David J. Graham.[1] *[1]U.S. Food and Drug Administration, Silver Spring, MD, USA; [2]Acumen LLC, Burlingame, CA, USA; [3]Centers for Medicare & Medicaid Services, Washington, DC, USA.*

Background: Studies have shown association of angioedema with ACEIs compared to beta-blockers and calcium channel inhibitors. Also, increased risk of angioedema in Blacks compared to Whites has been well documented. There are few studies of effect modification by race on drug-associated angioedema.

Objectives: This study aimed to assess association of ACEIs and ARBs with angioedema in enrollees in CMS Medicare, focusing on effect modification by race.

Methods: Beneficiaries were enrolled in new-user ACEI, ARB, or beta-blocker cohorts, provided that at their first eligible prescription (filled between March 2007 and March 2014), they were aged ≥65 years, were not in a nursing home or skilled nursing facility, and during the preceding 183 days, were continuously enrolled in Medicare parts A, B, and D, and had no dispensings of any study drug or diagnosis of angioedema (defined as ICD-9 code 995.1 in any care setting). Beneficiaries were followed until the first occurrence of either death, disenrollment from Medicare, cessation of drug use, or end of study period. Cox proportional hazards models with race–treatment interactions were used to examine the risk of angioedema for ACEIs and ARBs compared to beta-blockers.

Results: Incidence rates (per 1000 person years) of angioedema while exposed to beta-blockers were 1.80 among Whites, 1.89 among Asians, 2.10 among Hispanics, and 4.11 among Blacks, while the corresponding incidence rates for those exposed to ACEIs were 4.03, 2.94, 4.27, and 23.77. Results from Cox proportional hazards models show significant interaction terms for cohort *x* race for ACEIs and Black (2.59(2.24–2.99); $p < 0.001$) but not for other races. In contrast, cohort *x* race terms for ARBs were all non-significant. Occurrence of angioedema by length of drug exposure is also being examined.

Conclusions: In Medicare elderly, there is evidence suggesting effect modification by Black race when individuals exposed to ACEIs are compared with those exposed to beta-blockers, while this is not the case for ARBs compared to beta-blockers or for other race groups. This is the first study with sufficient power to examine this issue in multiple race groups.

547. Long-term Use of Calcium Channel Blockers, Beta-blockers, Angiotensin-receptor Blockade and Risk of Breast Cancer in Women Aged 55 Years or Older: A Nationwide Study

Chia-Hsuin Chang,[1,2] Li-Chiu Wu,[2] Chien-Hsieh Chiang,[3] Jou-Wei Lin,[4] Mei-Shu Lai.[2] *[1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [3]Department of Family Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Cardiovascular Center, National Taiwan University Hospital Yun-Lin Branch, Douliou City, Yunlin County, Taiwan.*

Background: There is a long debate about the potential breast cancer risk associated with use of calcium channel blockers.

Objectives: We aimed to specifically investigate the association of long duration use of anti-hypertensive

agents with incident breast cancer risk among women aged 55 years or older.

Methods: A total of 794 533 women aged ≥55 years were identified from Taiwan National Health Insurance claims database during 2001–2011. As of 31 December 2011, incident breast cancer patients were included as cases, and 1:4 age-matched controls were selected by risk-set sampling scheme. Logistic regression models were applied to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) between different duration of use of angiotensin-converting enzyme in. hibitors/angiotensin-receptor blockers (ACEI/ARBs), beta-blockers (BBs), dihydropyridine calcium channel blockers (DHP CCBs), and breast cancer incidence, adjusted for use of hormone replace therapy, insulin, oral diabetic agents, statins, and underlying diseases.

Results: Among the 9397 incident breast cancer patients and 37 588 controls, a significantly elevated risk was found for use of DHP CCBs for ≤2 years (adjusted OR: 1.28; 95%CI: 1.05–1.57), >2–4 years (adjusted OR: 1.37; 95%CI: 1.05–1.79), and >4 to 6 years (adjusted OR: 1.43; 95%CI: 1.02–2.01). No significantly increased risk was observed for DHP CCBs use for ≥6 years. In contrast, similar relation was not observed for ACEI/ARBs use nor observed for BBs use. While restricting our analyses to those with any prescription of study medications in 2001 or those with diagnosis of hypertension, a significantly increased breast cancer occurrence was no longer found for use of ACEI/ARBs, BBs, nor DHP CCBs.

Conclusions: The results did not suggest that there was a strong causal relation between long-term use of any anti-hypertensive agents, including DHP CCBs, and risk of breast cancer.

548. Bleeding Risks Are High in Elderly Persons Who Use Vitamin K Antagonists Combined with Platelet Aggregation Inhibitors

Nienke van Rein,[1,2,3] Uffe Heide-Jørgensen,[3] Willem M. Lijfering,[1,2,4] Lars Pedersen,[3] Olaf M. Dekkers,[3,4] Henrik T. Sørensen,[3] Suzanne C. Cannegieter.[4]
[1]Department of Thrombosis and Haemostasis, Leiden University Medical Center, Leiden, The Netherlands; [2]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands; [3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [4]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

Background: Patients with atrial fibrillation (AF) frequently require vitamin K antagonists (VKAs) and at times additional platelet aggregation inhibitors. Combining platelet aggregation inhibitors and VKAs increases the risk of major bleeds twofold to fourfold. This risk combined with the age-related increase in baseline bleeding risk may be a contraindication for combination therapy in elderly. However, data are lacking on absolute bleeding risks stratified by age.

Objectives: This study aimed to examine the bleeding risk for VKAs and/or platelet aggregation inhibitors in AF patients stratified by age.

Methods: This nationwide cohort study focused on Danish patients aged 50 years or older diagnosed with incident AF between 1995 and 2013. Seven exposure categories (based on a prescription database data) were considered: VKAs, aspirin, clopidogrel, dipyridamole, a combination of two platelet aggregation inhibitors, a platelet aggregation inhibitor combined with a VKA and triple therapy. Incidence rates (IRs) of major bleeds per 100 patient-years and 95% confidence intervals (CIs) were stratified by 10-year age categories.

Results: Of 238 555 AF patients, 207 085 (87%) filled at least one prescription for an anticoagulant. Major bleeds of 35 399 occurred during a follow-up of 1 015 511 patient-years. For monotherapy, the overall IR for bleeds was 1.78 (95%CI: 1.64–1.92) among patients aged 50–60 years. IRs increased to 4.79 (95%CI: 4.29–5.34) and 4.45 (95%CI: 4.20–4.72) for patients aged over 90 years taking VKAs and aspirin, respectively. Overall IRs during triple therapy were three to five times higher (IR range: 9.02–20.27) compared with VKA monotherapy. IRs for triple therapy were 14.18 (95%CI: 11.94–16.72) and 20.27 (95%CI: 11.78–32.68) for patients aged above 80 and 90 years, respectively.

Conclusions: Major bleeding rates are high in AF patients aged 80 years or older who receive triple therapy. To judge whether triple therapy is contraindicated in particular age groups, data are needed on its preventive effect on ischemic stroke.

549. Assessing Clinical Outcome of Aspirin Containing Magnesium Stearate for Acute Coronary Syndrome

Kelly Huang,[1] Chin-lan Cheng,[1,2] Jinding Huang,[1,2] Yea-Huei Kao Yang.[1,2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]School of Pharmacy, National Cheng Kung University, Tainan, Taiwan.*

Background: The physical/chemical interaction between active pharmaceutical ingredient (API) and excipients has been studied for pharmaceutical formulation. Although aspirin and magnesium stearate (MgSt, usually as lubricant in tablets or capsules) are one of the combinations noticed to avoid, there are some aspirin products containing MgSt available in market. Theoretically, too much lubricant could affect the uniformity of solid formulation, and magnesium cation might raise the pH value due to chemical reaction and further catalyze the hydrolysis of aspirin. Aspirin is the cornerstone medication for patients with acute coronary syndrome (ACS); however, the clinical outcome remains unknown in patients taking aspirin products containing MgSt.

Objectives: Our study hypothesis was that MgSt would affect the formulation and reduce the potency of aspirin, which may decrease the prevention effect for ACS recurrent. We aimed to compare the recurrent rate of ACS in patients taking aspirin products with and without MgSt (MgSt-ASA and ASA).

Methods: We conducted a nationwide, observational, and nested case–control study with Taiwan National Health Insurance Research Database (NHIRD). Cohort population enrolled patients who first hospitalized for ACS (ICD-9 code 410/411) during 2002–2008, who aged between 18 and 100 years. Definition of cases was recurrent admission for ACS. Controls group was 1:1 matched with age (±1), gender, and follow-up period. MgSt-ASA or ASA used on last 180 days of the study end point was analyzed. Adjusted odds ratios (OR) of recurrent ACS with current use of MgSt-ASA were estimated using conditional logistic regression.

Results: We identified 109 338 patients (aged 66.7 ± 13.1 years; 69% male) who had AMI hospitalizations between 2002 and 2008. There were 35 604 events before 2009, which 4787 events used MgSt-ASA. The incidences were 1.35 per person-year for MgSt-ASA and 1.16 per person-year for ASA. The crude odds ratio was 0.826 (0.557–1.225, 95%CI).

Conclusions: We are expecting the result to support or reject the theory of excipient compatibility with API, and further analysis will be carried out.

550. Epidemiologic Study on the Risk of Developing Depression in Association with Use of Beta-blockers or Other Cardiovascular Drugs

Delia C. Bornand,[1] Susan S. Jick,[2] Christoph R. Meier.[1,2] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA.*

Background: Case reports and previous studies provided evidence that beta-blockers may increase the risk of developing depression, but other studies refuted this hypothesis. There is a controversy whether the depression risk depends on physic-chemical properties of beta-blockers and whether depression may be the consequence of the cardiovascular indication, the lowering of the blood pressure, or a direct effect of these drugs on the central nervous system.

Objectives: It was the aim of the study to analyze the association between use of beta-blockers, other antihypertensive drugs, and the risk of developing depression.

Methods: We conducted a case–control study using the Clinical Practice Research Datalink (CPRD). We identified cases below the age of 80 years who had an incident diagnosis of depression between 2000 and 2009 and the same number of matched controls on age, sex, general practice, calendar time, and years of previous history in the database. Using conditional logistic regression analyses, we explored the association of cardiovascular drugs on the risk of developing depression and adjusted for several diseases, smoking status, and body mass index.

Results: We identified 72 969 patients with an incident depression diagnosis. We identified a higher relative risk of depression in patients with beta-blocker use (OR 1.67, 95%CI: 1.59–1.76), especially for lipophilic beta-blockers without cardioselectivity. A recent beginning of beta-blocker use augmented the OR to 2.62 (95%CI: 2.38–2.88), and a recent beginning of lipophilic beta-blocker use even increased the OR to 3.38 (95%CI: 3.00–3.80). Other cardiovascular drugs also yielded a small but significant increased OR for depression: ACE inhibitors (OR: 1.36, 95%CI: 1.17–1.58), AT2 antagonists (OR: 1.31, 95%CI: 1.12–1.53), and diuretics (OR: 1.36, 95%CI: 1.27–1.47).

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Conclusions: In this case–control study, we found an increased risk of developing depression associated with use of beta-blockers. The data suggest that different physic-chemical properties of beta-blockers may be associated with different depression risks, especially in the early phase of a therapy.

551. Lipophilic Statins and the Risk of Suicide: A Population-based Study

Jessica L. S. Leen,[1] Erin M. MacDonald,[2] Simon Hollands,[2] Muhammad M. Mamdani,[2,3,4,5,6] J Michael Paterson,[2,4,7] David N. Juurlink.[1,2,4,8] *[1]Department of Medicine, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada; [5]Applied Health Research Centre, St. Michael's Hospital, Toronto, ON, Canada; [6]King Saud University, Riyadh, Saudi Arabia; [7]Department of Family Medicine, McMaster University, Hamilton, ON, Canada; [8]Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Background: Statins influence cholesterol synthesis in the brain. Limited data suggest that this may affect behavior, possibly increasing the risk of depression or suicide. Whether lipophilic statins, which cross the blood–brain barrier more readily, confer greater risk of suicide is unknown.

Objectives: This study aimed to explore the association between lipophilic statins and suicide.

Methods: We conducted a population-based case–control study using data from multiple linked healthcare databases of patients from Ontario, Canada, between 1 January 1993 and 31 December 2012. Cases were adults aged 66 years and older who died of suicide within 100 days of receiving a statin. For each case, we identified four age-matched and sex-matched control subjects who were treated with a statin but did not die of suicide. Statins were classified as lipophilic (atorvastatin, fluvastatin, lovastatin, cerivastatin and simvastatin) or hydrophilic (pravastatin and rosuvastatin) based on their octanol/water partition coefficients. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were estimated for the association between suicide and lipophilic statin use, with hydrophilic statins as the reference group.

Results: We identified 536 cases who died of suicide within 100 days of receiving a prescription for a single statin, along with 2144 matched controls. In the primary analysis, lipophilic statins were associated with an increased risk of suicide (adjusted OR: 1.42; 95% CI: 1.09–1.85) relative to hydrophilic statins.

Conclusions: Lipophilic statins may be associated with an increased risk of suicide in the elderly. Given the widespread use of statins and the increased risk of elder suicide, confirmation of these novel findings would have important implications for public health.

552. Use of Nicorandil Is Associated with Increased Risk for Gastrointestinal Ulceration and Perforation—A Nationally Representative Population-based Study

Meng-tse Gabriel Lee,[1] Shih-Hao Lee,[1] Yueh-Sheng Chen,[2] Xia-Dong Xia,[3] Shy-Shin Chang,[4] Chien-Chang Lee.[5] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Diagnostic Radiology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [3]Department of Electrical and Computer Engineering, University of Miami, Coral Gables, FL, USA; [4]Department of Family Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan; [5]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou, Taiwan.*

Background: Nicorandil is a vasodilatory drug commonly used to relieve angina symptoms. Recently, several healthcare products regulatory agencies have issued a warning associating the use of nicorandil and gastrointestinal (GI) ulceration.

Objectives: The aim of this study was to evaluate the association between use of nicorandil and GI ulceration/perforation in a national representative cohort.

Methods: We carried out a population-based cohort study involving 1 million randomly sampled participants in Taiwan's National Health Insurance Research Database. These participants were longitudinally followed from January 2005 to December 2009. We estimated the association between use of nicorandil and GI ulceration/perforation by a Cox proportional hazards regression model. A nicorandil-specific propensity score (PS) was also created for adjustment of 75 covariates and matching.

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Results: Of nicorandil-treated patients, 25.8% (183/710) developed new GI ulcer events, and 1.6% (20/1254) developed new GI perforation events in the 3-year follow-up period, as compared to 9.3% (61 281/659 081) and 0.3% (2488/770 537) in the general population comparator cohort. Patients treated with nicorandil were at significantly increased risk of GI ulceration (PS adjusted hazard ratio 1.43, 95%CI: 1.23–1.65, and 6848 excess cases per 100 000 person years) or GI perforation (aHR: 1.60, 95%CI: 1.02–2.51, and 315 excess cases per 100 000 person years) compared with the nicorandil-unexposed population. In subgroup analysis, we also found that elderly patients and females carried a higher risk for GI ulceration.

Conclusions: Overall, nicorandil-treated patients have a 43% increase in relative risk of GI ulceration and a 60% increase in relative risk of GI perforation compared with nicorandil-untreated patients. Given the substantial increase in absolute risk, these finding may warn the clinicians to weigh the overall risk-benefit balance of nicorandil treatment in patients at high risk for GI ulceration or perforation.

553. Use of Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and Risk of Ileus among a Type 2 Diabetes Mellitus (T2DM) Population: A Retrospective Cohort Study in Japan

Dimitri Bennett,[1] Shreya Davé,[2] Motonobu Sakaguchi,[3] Chia-Hsien Chang,[3] Paul Dolin.[2] *[1]Global Pharmacovigilance, Takeda Development Centre US Ltd, Cambridge, MA, USA; [2]Global Pharmacovigilance, Takeda Development Centre Europe Ltd, London, UK; [3]Global Pharmacovigilance, Takeda Pharmaceutical Company Limited, Osaka, Japan.*

Background: Ileus is a form of non-mechanical bowel obstruction. A recent literature report of three cases of ileus in DPP-4 inhibitors-treated patients in Japan has triggered this epidemiology study to quantify and assess the risk.

Objectives: This study aimed to quantify the incidence rate of ileus among T2DM patients that were new users of alogliptin, other DPP-4 inhibitors, glucagon-like polypeptide-1 (GLP-1) receptor agonists and voglibose.

Methods: The study design was a retrospective cohort study using a Japanese Medical Data Vision (MDV) claims database. The study population was T2DM patients who were new users of alogliptin, other DPP-4 inhibitors, GLP-1 receptor agonists, or voglibose between 01/04/2010 and 30/04/2014. New users were defined as patients without any previous prescriptions for medications of interest before cohort entry.

Patients were aged 40+ years at cohort entry and were followed up until the earliest of incident diagnosis of ileus or the earliest of the last prescription date of the first therapy episode or day before date of treatment switch/add-on. Incidence rates of ileus were assessed, both overall and by risk time window. Poisson regression models assessed incidence rate ratios (IRR) for ileus with 95% confidence intervals (95%CI). This abstract is based on preliminary data. Final results will be presented at the meeting.

Results: $N = 82\,470$ T2DM patients were identified in the database, of whom $N = 9669$ (11.72%), $N = 55\,954$ (67.85%), $N = 1906$ (2.31%), and $N = 14\,941$ (18.12%) were new users of alogliptin, other DPP-4 inhibitors, a GLP-1 receptor agonists, and voglibose, respectively. Preliminary results showed that overall incidence of ileus was 9.05 per 1000 pyrs (95%CI: 7.36–11.12) for alogliptin, 10.29 per 1000 pyrs (95% CI: 9.52–11.11) for other DPP-4 inhibitors, 32.16 per 1000 pyrs (95%CI: 14.45–71.59) for GLP-1 receptor agonists, and 12.17 per 1000 pyrs (95%CI: 10.58–14.00) for voglibose.

Conclusions: Unadjusted incidence rates of ileus among users of alogliptin and other DPP-4 inhibitors were similar, while the rate for users of GLP-1 receptor agonists was higher.

554. Safety Experience in New Oral Anticoagulant Use in Patients with Non-valvular Atrial Fibrillation—Data from One-year Post-launch

Han-Yao Huang,[1] Hugh Kawabata.[2] *[1]Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb, Pennington, NJ, USA; [2]Center for Observational Research and Data Science, Bristol-Myers Squibb, Pennington, NJ, USA.*

Background: Several new oral anticoagulants (NOACs) were recently made available for stroke risk reductions for patients with non-valvular atrial fibrillation (NVAF). An important safety concern over these drugs is bleeding risks.

Objectives: This study aimed to assess bleeding risks of NOACs and warfarin in NVAF in the USA.

Methods: An active surveillance program was conducted using MarketScan claims data from NVAF adults treated with NOACs in the first-year post-launch of each NOAC or treated with warfarin in the corresponding periods. Incidence rates of bleeds as the primary hospital discharge codes were calculated based on cumulative data since launch to the end of each quarter.

Results: A total of 3752 apixaban, 13 264 dabigatran, and 6527 rivaroxaban users in the first-year post-launch and 27 314, 34 744, and 32 139 warfarin users in the corresponding periods were eligible for analyses.

Compared to warfarin users, NOACs users were younger and had lower CHADS2 and prior NSAIDs use and were less likely to have thrombotic/bleeding history and co-morbidity. NOACs user characteristics were similar except that age 75+ and CHADS2 3+ were 3–8% more frequent in apixaban users.

At the end of each quarter of 2013, incidence rates (95%CIs) (per 100 person-year) of bleeds were 4.0 (2.8–5.5), 3.9(3.2–4.7), 3.7(3.2–4.3), and 3.8(3.4–4.3) for warfarin and 0, 0.9(0.02–5.02), 1.4(0.5–3.4), and 1.4(0.7–2.6) for apixaban. In October 2010 to September 2011, the rates were 4.0(2.8–5.4), 4.5 (3.7–5.3), 4.2(3.7–4.8), and 3.8(3.4–4.3) for warfarin and 4.2(0.9–12.2), 3.3(2.0–5.2), 2.7(2.0–3.6), and 2.5(2.0–3.2) for dabigatran. In November 2011 to October 2012, the rates were 2.7(1.7–4.1), 3.7(3.0–4.5), 3.6(3.1–4.1), and 3.4(3.0–3.8) for warfarin and 6.8 (0.8–24.7), 4.5(2.1–8.2), 3.1(1.9–4.7), and 3.0(2.1–4.0) for rivaroxaban. A similar pattern was observed with the rates of gastrointestinal bleeds. Rates of intracranial bleeds were lower with NOACs than warfarin.

Conclusions: Although safety experience in apixaban was limited, crude bleeding rates appeared lower in apixaban users than users of other oral anticoagulants. Multivariate analyses await additional data accrual.

555. Statin-related Muscle Problems: Prevalence and Therapeutic Response

Donald R. Miller,[1] Kyung Lee,[1] Adam Rose,[1] Varsha Vimalananda,[1] Cindy L. Christiansen.[1] [1]*Center for Healthcare Organization and Implementation Research, Bedford VA Medical Center, Bedford, MA, USA.*

Background: HMG Co-reductase Inhibitors (statins) are highly effective in primary and secondary prevention of cardiovascular disease, but poor adherence to statin regimens often develops over time. Muscle pain and weakness has been reported by patients receiving statins, and this may contribute to lack of persistence on statins. Published estimates of the prevalence of reported statin-related muscle problems vary widely, and therapeutic responses to these problems have not been well studied.

Objectives: This study aimed to estimate the frequency of incident muscle problems among statin users in a large clinical patient population and evaluate how they may contribute to reduced treatment intensity and discontinuation.

Methods: We studied veterans receiving health care from the US Dept. of Veteran Affairs (VA) and with VA prescriptions for statins in 2009. Among those with first statin prescription in that year, we used ICD-9-CM codes to identify and exclude those with prevalent muscle problems, including rhabdomyolysis, myalgia, myositis, myopathy, and symptoms of muscle pain or weakness. We then examined subsequent clinic and hospital records of remaining patients for incident muscle problems and prescription records for changes in statin regimen.

Results: Statins were prescribed to over 2.1 million VA patients (48%) in 2009, with simvastatin as the predominant agent (82%). After limiting the sample to those with first statin prescription in that year and without codes for muscle problems in the prior 2 years, we found that 11.6% of patients have new codes for muscle problems in the 2 years following first prescription. This rate varied among the agents from 9.7% for lovastatin to 14.9% for atorvastatin. More than half of these patients (53.3%) were not prescribed with statins subsequently, and only 5% switched agents. Women tended to have muscle problems on statins more often than men (17.0% vs 11.3%), but therapeutic responses were similar.

Conclusions: Statin-related muscle problems are common in veteran patients and often lead to discontinuation of statin therapy. This adverse drug effect appears to have a substantial impact in reducing the potential benefits of statin use in cardiovascular disease prevention.

556. Preadmission Diuretic Use Is Associated with 30-day and 1-year Mortality in Patients with Hyponatremia

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Louise Holland-Bill,[1] Christian F. Christiansen,[1] Sinna P. Ulrichsen,[1] Troels Ring,[2] Jens Otto L. Jørgensen,[3] Henrik T. Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark; [3]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark.*

Background: While diuretics are a leading cause of hyponatremia, the prognostic impact of diuretic use in hyponatremic patients is unknown.

Objectives: The aim of this study was to examine 30-day and 1-year mortality in diuretic users and non-users hospitalized with hyponatremia.

Methods: We conducted a propensity score (PS)-matched cohort study among 328 166 patients acutely admitted to the Departments of Internal Medicine in the North and Central Denmark Regions from 2006 to 2012, using prospectively collected data from population-based medical registries (population ~2 million). We included 30 721 patients with a serum sodium measurement <135 mmol/l within 24 hours following admission. Current diuretic users were defined as patients who redeemed a prescription for any diuretic within 90 days before admission and were considered new users if this was the first prescription for diuretics since 1 January 2004. We calculated each patient's PS based on age, gender, previous morbidity, baseline estimated glomerular filtration rate and co-medication and performed 1:1 matching without replacement of current users to the nearest non-user (maximum caliper range of ±0.025). We computed 30-day and 1-year mortality using the Kaplan–Meier method and relative risk (RR) using pseudo-value regression, accounting for matched pairs. We repeated the analyses by type of diuretic.

Results: The PS-matched analysis included 9493 current users (78.7% of all current users) and 9.493 non-users. Thirty-day mortality was 7.9% in non-users and 10.7% in current users, corresponding to a RR of 1.4 (95%CI: 1.2–1.5). For new and long-term users, the RRs were 1.7 (95%CI: 1.5–2.0) and 1.3 (95%CI: 1.2–1.4), respectively. The highest risk was observed among users of loop diuretics (*RR* = 1.8 (95%CI: 1.6–2.1)), potassium-sparing diuretics (*RR* = 1.7 (95%CI: 1.3–2.4)) and diuretic polytherapy (*RR* = 1.7 (95%CI: 1.5–2.0)), while thiazide users had a RR of 1.0 (95% CI: 0.9–1.2). The risk remained elevated after 1 year (*RR* = 1.2 (95%CI: 1.2–1.3)).

Conclusions: Newly initiated diuretic use, use of loop and potassium-sparing diuretics and diuretic polytherapy were associated increased 30-day and 1-year mortality in patients with hyponatremia.

557. Cataract Risk after Exposure to Angiotensin-converting-enzyme Inhibitors: A Case–Control Analysis

Claudia Becker,[1] Susan S. Jick,[2] Christoph R. Meier.[1,2,3] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA; [3]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland.*

Background: Angiotensin-converting-enzyme inhibitors (ACEI) have endothelial pleiotropic actions and can modulate glucose control. They have been hypothesized to lower the risk of cataract in diabetic patients. Animal studies showed a delayed diabetic cataract development after ACEI exposure. However, in an observational study, cataract risk in ACEI users was increased (OR: 1.54; 95%CI: 1.01–2.36).

Objectives: This study aimed to explore the association between use of ACEI and risk of cataract.

Methods: We conducted a case–control analysis within the UK-based Clinical Practice Research Datalink (CPRD). Cases were ≥40 years and had either an incident cataract diagnosis or a cataract extraction (i.e., the index date). Up to four controls per case were matched on age, sex, calendar time, general practice, and number of years of history in the CPRD prior to the index date. We assessed the number of ACEI prescriptions before the index date and conducted conditional logistic regression to derive odds ratios (ORs) with 95% confidence intervals (CI). The contribution of various potential confounders including co-morbid conditions and exposure to other drugs previously associated with cataract development was evaluated in univariate models. Final results were adjusted for BMI, smoking, hypertension, diabetes, glaucoma, oral steroids, and other antihypertensive drugs. We performed a separate analysis in diabetic cases only, matched to diabetic controls, using the same multivariate model, but adjusting for diabetes duration instead of diabetes diagnosis.

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Results: A total of 158 679 cataract cases and 564 787 matched controls were included in the main analysis. Long-term use (≥40 prescriptions) of ACEI was not associated with an altered cataract risk (adj. OR: 1.05; 95%CI: 1.02–1.07). Mutually exclusive exposure for separate ACEI yielded a slightly decreased risk for captopril (adj. OR: 0.90; 95%CI: 0.85–0.95) as observed in previous animal studies. The analysis in diabetic patients (28 245 cases and 91 383 controls) showed similar results (long-term ACEI exposure: adj. OR: 1.12; 95%CI: 1.07–1.16).

Conclusions: In our study, we did not observe a substantial influence of long-term ACEI use on cataract risk.

558. Cardiovascular Drugs and Erectile Dysfunction—A Symmetry Analysis

Lotte Rasmussen,[1] Jesper Hallas,[1] Kenneth Grønkjær Madsen,[1] Anton Pottegård.[1] *[1]Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark.*

Background: Erectile dysfunction (ED) is a common problem among patients with cardiovascular diseases, and the influence of cardiovascular drugs is much debated.

Objectives: The aim of this study was to evaluate the short-term potential for different cardiovascular drugs to affect the risk of being prescribed a drug against erectile dysfunction.

Methods: We employed a symmetry analysis design and included all Danish male subjects born before 1950 who redeemed their first ever prescription for a cardiovascular drug and a 5-phospodiesterase inhibitor within a 6-month interval during 2002–2012. If the cardiovascular drug induces erectile dysfunction, this would manifest as a non-symmetrical distribution of subjects being prescribed the cardiovascular drug first versus persons following the opposite pattern. Furthermore, we calculated the number of patients needed to treat for one additional patient to be treated for erectile dysfunction (NNTH).

Results: We identified 27 551 male subjects who initiated a cardiovascular drug and a 5-phosphodiesterase inhibitor within a 6-month interval. Sequence ratios showed minor asymmetry in prescription orders after adjustment for trends in prescribing. This asymmetry was most profound for thiazides (1.28; 95%CI: 1.20–1.38), calcium channel blockers (1.29; 1.21–1.38) and ACE inhibitors (1.29; 95%CI: 1.21–1.37), suggesting a small liability of these drugs to provoke ED. NNTH values were generally large, corresponding to a generally small absolute effect.

Conclusions: Our study does not suggest that cardiovascular drugs strongly affect the risk of being prescribed a drug against erectile dysfunction on a short-term basis.

559. Pattern of Risks of Systemic Lupus Erythematosus among Statin Users: A Population-based Retrospective Cohort Study

Hilda J. De Jong,[1,2] Tjeerd P. Van Staa,[3,4,5] Arief Lalmohamed,[3,6] Rob J. Vandebriel,[7] Henk Van Loveren,[2,7] Frank De Vries,[2,3] Olaf H. Klungel,[3] Jan Willem Cohen Tervaert.[2,8] *[1]University of British Columbia, Vancouver, Canada; [2]Maastricht University Medical Centre, Maastricht, The Netherlands; [3]Utrecht University, Utrecht, The Netherlands; [4]University of Manchester, Manchester, UK; [5]London School of Hygiene & Tropical Medicine, London, UK; [6]University Medical Centre Utrecht, Utrecht, The Netherlands; [7]National Institute for Public Health and the Environment, Bilthoven, The Netherlands; [8]Sint Franciscus Gasthuis, Rotterdam, The Netherlands.*

Background: Statins are widely prescribed drugs to reduce the risk of cardiovascular morbidity and mortality. Besides their cholesterol-lowering activity, statins exert anti-inflammatory and immunomodulatory effects and may suppress the expression of ongoing autoimmune responses, for example, systemic lupus erythematosus (SLE). The immunomodulating effects may, on the other hand, facilitate the development of autoimmunity potentially resulting in autoimmune diseases, such as SLE. It is unclear whether statin use is associated with the risk of developing SLE.

Objectives: We examined the association between the use of statins and the risk of SLE, with a special focus on describing the patterns of risks of SLE with changes in statin exposure over time.

Methods: A retrospective cohort study using the UK Clinical Practice Research Datalink was conducted. All patients aged 40 years or older, who had at least one prescription of statins during the period of 1995–2009, were selected and matched by age, sex, practice

and date of first prescription of statins to controls (non-users). The follow-up period of statin users was divided into periods of current, recent and past exposure, with patients moving between these three exposure categories over time. All patients were followed up for SLE. Time-dependent Cox models were used to calculate hazard ratios (HRs) of SLE, adjusted for smoking, the history of hyperlipidaemia, hypertension, diabetes, cardiovascular and cerebrovascular diseases and previous nonsteroidal anti-inflammatory drug (NSAID) use.

Results: We included 1 039 694 patients, of whom 519 847 were statin users. No association was found between current exposure to statins and the risk of SLE. However, a 3.4-fold increased risk of SLE was found for recent users of statins (adj HR: 3.40; 95%CI: 1.83–6.30) and a 2.5-fold elevated risk of SLE for past users (adj HR: 2.50; 95%CI: 1.63–3.84), compared to controls.

Conclusions: Our findings do not support an association between current statin use and the risk of SLE. However, our findings show that discontinuation of statin treatment is associated with an increased risk of SLE.

560. Risk of Skin Ulcerations Associated with Oral Nicorandil Therapy—A Population-based Study

Chien-Chang Lee,[1] Hsin-Yi Lin,[2] Meng-tse Gabriel Lee,[3] Shih-Hao Lee,[3] Sie-Huei Lee,[4] Shy-Shin Chang,[5] Hsiung-Wen Vennia Chang,[6] Shyr-Chyr Chen.[3] *[1]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou, Taiwan; [2]Taipei Medical University—Shuang Ho Hospital, Taipei, Taiwan; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]Taipei Veteran General, Taipei, Taiwan; [5]Chang Gung Memorial Hospital, Taoyuan, Taiwan; [6]Taipei Municipal Wan Fang Hospital, Taipei, Taiwan.*

Background: Although healthcare products regulatory agencies have issued warnings on risk of ulcerations associated with use of nicorandil, a population-based study has never been carried out.

Objectives: We aimed to determine the relationship between use of nicorandil and skin ulceration.

Methods: We carried out a population-based study using a 1 million cohort assembled from Taiwan's national health insurance database. The association between nicorandil use and skin ulcers was estimated by logistic regression analysis adjusting for a nicorandil-specific propensity score (PS) composing of 86 potential predictors (C-statistics: 0.91).

Results: The prospective cohort was longitudinally followed from January 2005 to December 2009, during which a total of 1268 new users of nicorandil and 71 136 non-users were identified. A higher frequency of skin ulcers (29/1268 = 2.3%) was observed for users of nicorandil as compared to non-users (3231/771 136 = 0.4%). Compared with non-users, the crude odds ratio associating nicorandil use with skin ulcers was 5.56 (95%CI, 3.84–8.05), and the PS-adjusted odds ratio was 1.87(95%CI, 1.27–2.75). A risk period analysis by a hazard function plot showed that the risk of skin ulceration among nicorandil users was greatest on the first year. Subgroup analysis suggested that participants ≤75 years of age and male users of nicorandil had higher risk of skin ulceration.

Conclusions: Use of nicorandil was found to be associated with increased risk for skin ulceration, especially in the first year after incident exposure. We suggest that healthcare products regulatory agencies re-evaluate the risk for skin ulceration associated with use of nicorandil.

561. Effect of Non-technological Interventions on Medication Errors in Cardiology

Mariana Molina,[1] Carolina Lobos,[1] Pia Cárcamo,[1] Marcela Jirón.[1] *[1]Ciencias y Tecnologia Farmaceutica, Facultad de Ciencias Quimicas y Farmaceuticas, University of Chile, Santiago, Chile.*

Background: Medication errors (MEs) are common among cardiovascular drugs, limiting the effectiveness and safety of pharmacological therapies in patients.

Objectives: The purpose of this study was to determine the effect of a Non-technological Interventions Program (NIP) on MEs frequency in a Cardiology Department (CD).

Methods: A prospective before–after study was conducted in a sample of 71 adult patients in a CD. An observational baseline and post-intervention assessment of the MEs frequency was performed over a control group and post-intervention group, respectively. Each patient was randomly selected. Direct observation was used to detect ME. Each medication process was compared with what the prescriber ordered; if there was a difference, the error was described and

categorized. A NIP (bundle of non-technological interventions to reduce MEs, i.e., education on safety and quality of drug use, standardized operation procedures on drugs administration and preparation, and voluntary report system) was implemented by a multidisciplinary team only in the CD after the baseline assessment. All medication prescriptions, transcriptions, dispensing, preparations, and administrations were assessed before and after NIP by independent pharmacists. MEs were defined according to the National Coordinating Council for Medication Error Reporting and Prevention.

Results: A total of 167 drugs for 37 control patients and 267 drugs for 34 post-intervention patients were assessed. The 71.8% of the sample were men; the mean age and Charlson index were 64.2 ± 12.4 years and 4.6 ± 2.3 points, respectively. The implementation of the NIP resulted in a 29.1% decrease on MEs frequency (49.1–34.8%; $p < 0.05$). Main variations of MEs frequency were seen on dispensing and administration process (66.7% and 38.8% of reduction in each stage, respectively). MEs were more common in two or more drugs administered concurrently.

Conclusions: The implementation of NIP by a multidisciplinary team resulted in a significant reduction of MEs frequency at an adult CD. Future multicenter randomized clinical trials should be conducted to determine the efficacy of NIP.

562. Safety of Aspirin for Cardiovascular Disease in China: A Systematic Review and Meta-analysis

Lin Zhuo,[1] Yinchu Cheng,[1] Yang Zhang.[1] *[1]Department of Epidemiology and Bio-statistics, Peking University Health Science Center, Beijing, China.*

Background: Aspirin is recommended for cardiovascular events, which are the leading causes of deaths in China.

Objectives: The purpose of this study was to assess the safety of aspirin for cardiovascular disease in China.

Methods: PubMed, Embase, and four Chinese electronic databases were searched from inception through 31 August 2014 with the keywords including "aspirin" for patients with cardiovascular disease. Quality assessment and information extraction were done by two independent screening. The quality of the included documents was evaluated by the Cochrane Collaboration's tool, NOS, MINORS for assessing risk of bias and allocation concealment. Revman 5.3, MetaAnalyst 3.1 software, was used for data analysis using random-effects model.

Results: A total of 239 articles were included, of which 163 were clinical trials. The total incidence of adverse gastrointestinal events in patients taking aspirin was 9.9%, and bleeding events were 6.1% including gastrointestinal bleeding 3.4% and intracranial bleeding 1.8%. Compared with normal treatment measures in clinical trials, the incidence of gastrointestinal events in patients taking aspirin was 7.48%, significantly higher than other drugs (4.84%) (OR = 2.16, 95%CI: 1.55–3.01, $p < 0.001$). The incidence of total bleeding events in aspirin group was 2.67%, higher than others (2.33%) (OR = 1.02, 95% CI: 0.85–1.22, $p > 0.05$). Especially, the incidence of gastrointestinal bleeding events was higher in the patients taking aspirin (2.41%) than other drugs (1.19%) (OR = 2.16, 95%CI: 1.55–3.01, $p < 0.05$).In 40 case reports, of them 28 were with bleeding events including 20 gastrointestinal bleeding. Leukopenia, gastrointestinal events, dental ulcer, and limb swelling were in two cases. Rash and renal dysfunction were in one case, respectively.

Conclusions: Having multiple types and large quantity, adverse reaction caused by aspirin is given priority to with gastrointestinal symptoms, but intracranial hemorrhage is rare. However, due to the small sample size and of lower quality, conclusions above still need more high-quality trials to be confirmed. Reaction monitoring should be strengthened for providing high-quality evidence for clinical application of aspirin in China.

563. The Effect of Antiarrhythmics on QT Variability in a Population-based Cohort of Middle-aged and Elderly Persons

Marten E. van den Berg,[1] Maartje N. Niemeijer,[2] Bruno H. Stricker,[2] Mark Eijgelsheim,[3] Jan A. Kors,[1] Peter R. Rijnbeek.[1] *[1]Medical Informatics, Erasmus MC, Rotterdam, Zuid-Holland, The Netherlands; [2]Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, The Netherlands; [3]UMCG, Groningen, The Netherlands.*

Background: QT variability is a promising risk marker for ventricular arrhythmias and sudden cardiac

death. To date, the association of cardiovascular drugs with QT variability has been studied in animal studies or studies with a small number of participants.

Objectives: The aim was to study the association of the antiarrhythmics amiodarone, digoxin, flecainide and sotalol with QT variability, using verapamil as a negative control.

Methods: We used data from a prospective population-based cohort. Drug use during electrocardiogram (ECG) was obtained from pharmacy records. Participants with at least two 12-lead ECGs recorded were included. We used generalized estimation equations to model the association between drug use and the change in short-term QT variability (STVqt) between two consecutive ECGs. STVqt was calculated in means with fiducial segment averaging. Exposure was categorized as nonuse of a drug at both ECGs (reference), use at only the first or the second and use at both ECGs. All analyses were adjusted for age, sex, heart rate, heart-rate variability and QT interval at the first ECG.

Results: We included 4958 participants (58% women) with 10 284 pairs of ECG recordings. Mean time between visits was 4.1 years. Mean age at study entry was 64.7 years (standard deviation 9.7); median STVqt on the first ECG was 2.26 milliseconds (interquartile range 1.41; 3.93). Compared with nonusers during of both ECG recordings, the change in STVqt was significantly higher in participants who used amiodarone (2.27 milliseconds, 95% confidence interval (CI) 0.10; 4.44), digoxin (2.59 milliseconds, 95%CI: 0.51; 4.67) flecainide (3.39 milliseconds, 95%CI: 1.26; 5.52) or sotalol (3.03 milliseconds, 95%CI: 1.17; 4.90) at the second ECG. STVqt was significantly decreased users of amiodarone at the first ECG compared with nonusers at both ECGs (−2.53 milliseconds, 95% CI: −4.84; −0.22). The change in STVqt did not differ significantly from nonuse at both ECGs when verapamil was used at either ECG.

Conclusions: Our population-based study shows that STVqt is significantly increased in participants changing from nonuse to use of sotalol, amiodarone, flecainide and digoxin but not of verapamil, which is in line with previous animal studies.

564. Epidemiological Evidence on Associations between Statin Use and Lymphoid Malignancy Incidence Risk and Survival

Xibiao Ye,[1] Ayat Mneina,[1] James Johnston,[2] Salaheddin Mahmud.[1] *[1]University of Manitoba, Winnipeg, MB, Canada; [2]CancerCare Manitoba, Winnipeg, MB, Canada.*

Background: There is increasing epidemiological evidence on the chemopreventive effects of statins for several solid cancers (e.g., prostate and colorectal cancers), but evidence for their value in hematological malignancies is less clear. Moreover, a recent laboratory study has demonstrated that statin use might reduce the effectiveness of rituximab treatment for non-Hodgkin lymphoma (NHL), suggesting that statin use may influence the survival of NHL patients.

Objectives: This study aimed to examine the strength of scientific evidence concerning the impacts of statin use on lymphoma incidence risk and survival.

Methods: We conducted a systematic review and meta-analysis of studies on the impacts of statin use on two outcomes: lymphoma incidence risk and survival. We searched 11 electronic literature databases and clinical trial registers to identify observational studies and randomized clinical trials (RCTs) published prior to July 2014. We used a random effects model to calculate pooled odds ratio (PORs) for incidence risk and pooled hazard ratio (PHR) for survival. Heterogeneity among studies was examined using the Tau-squared and the *I*-squared (I^2) tests; sources of heterogeneity were explored using subgroup and meta-regression analyses.

Results: We identified 15 studies (five case–control studies, eight cohort studies, and two RCTs) on incidence risk and nine studies (eight cohort studies and one RCT) on survival. Statin use was associated with reduced incidence risk of lymphoma overall (POR = 0.83, 95%CI: 0.68–1.00) and NHL (POR = 0.83, 95%CI: 0.68–1.01). Analysis by NHL subtype found associations between statin use and lower incidence risk of diffuse large B-cell lymphoma (DLBCL) (POR = 0.72, 95%CI: 0.52–0.99) and marginal zone lymphoma (POR = 0.54, 95%CI: 0.31–0.94) but not other subtypes. However, statin use did not affect overall survival (PHR = 1.02, 95%CI: 0.99–1.06) or event-free survival (PHR = 0.99, 95% CI: 0.87–1.12) in DLBCL. No meta-analyses were undertaken for the survival of patients with other subtypes due to the lack of data.

Conclusions: There is suggestive epidemiological evidence that statins reduce the incidence risk of certain NHL subtypes but may not affect NHL patient survival.

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565. The Association of Hormone Therapy and Incident Gout: Population-based Case–Control Study

Saskia G. Bruderer,[1,2] Michael Bodmer,[3] Susan S. Jick,[4] Christoph R. Meier.[1,2,4] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Division of General Internal Medicine, Bern University Hospital, Inselspital, Bern, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA.*

Background: Gout risk increases in women, especially after menopause. This led to the notion that menopausal changes in serum levels of female sex hormones may be linked to increasing urate levels and gout risk and that female sex hormones may protect against the development of gout. Investigations showed that both estrogens and progestogens stimulate renal clearance of uric acid and thereby decrease serum urate levels.

Objectives: This study aimed to assess the odds of developing incident gout in association with use of postmenopausal estrogen plus progestogen therapy or estrogen alone, according to type, timing, duration, and route administration.

Methods: We conducted a retrospective population-based case–control analysis using the UK-based Clinical Practice Research Datalink. We identified female patients aged ≥45 years with incident gout between 1990 and 2010. We matched one female control to each case on age, general practice, calendar time, and years of active history in the database. We used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for confounders.

Results: Adjusted ORs of gout for current use of oral formulations of opposed estrogens (estrogen plus progestogen) were 0.69 (95%CI: 0.56–0.86) compared to never use. Current use was associated with a decreased odds ratio of gout in patients without renal failure (adj. OR: 0.71, 95%CI: 0.57–0.87) and with hypertension (adj. OR: 0.62, 95%CI: 0.44–0.87), compared to never use. Tibolone was associated with a decreased OR (adj. OR: 0.77, 95%CI: 0.63–0.95) for incident gout compared to never use. Estrogens alone did not alter the odds of developing gout.

Conclusions: Current use of oral opposed, but not of unopposed estrogens, was associated with a decreased odds ratio of incident gout in patients without renal failure, and it was more pronounced in patients with hypertension. Furthermore, use of tibolone, a synthetic steroid with metabolites that have estrogenic, androgenic, and progestogenic properties, was associated with a decreased OR of incident gout. The decreased OR of gout associated with EPT and with tibolone use may be related to the progestogen rather than the estrogen component.

566. Cardiovascular Disease Risk and Androgen Deprivation Therapy in Patients with Localized Prostate Cancer

Reina Haque,[1] Xiaoqing Xu,[1] Marianne Ulcickas Yood,[2] Andrea E. Cassidy-Bushrow,[3] Stephen K. Van Den Eeden,[4] Arnold L. Potosky.[5] *[1]Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA; [2]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; [3]Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, USA; [4]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; [5]Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, USA.*

Background: Scant information exists regarding the adverse effects of ADT (androgen deprivation therapy) on cardiovascular disease (CVD) risk among men with localized prostate cancer. As ADT is increasingly being used as primary mono-therapy in such men who undergo conservative treatment, information on adverse cardiac events is critically needed for optimal treatment decision-making.

Objectives: Our goal was to examine the association between primary ADT use and the risk of incident CVD among patients with localized prostate cancer.

Methods: We conducted a population-based cohort study using comprehensive electronic health records and cancer registry data from the Kaiser Permanente Southern California health plan. All men with newly diagnosed localized prostate cancer (1995–2008), who were not treated with curative intent therapy, and without evidence of CVD at baseline were followed for up to 16 years, through December 2010 ($n = 7587$). We examined 10 individual CVD events as our primary outcomes, as well as a composite of these outcomes. Cox

proportional hazard models with time-varying treatment variables and other covariates were used to assess the direct effect of primary ADT use (administered within 12 months of initial diagnosis) on the time to developing each incident CVD event and the composite CVD events. Race/ethnicity, age, and tumor characteristics, CVD medication use, and CVD risk factors were captured and adjusted to account for confounding by indication.

Results: Of the 7587 prostate cancer survivors, nearly 40% of men who did not receive any curative intent therapy initiated ADT within 12 months following initial diagnosis. Rates for each of the 10 individual outcomes were higher for men treated with ADT than for men not exposed to ADT. ADT was associated with increased risk of heart failure (adjusted HR = 1.30, 95%CI: 1.09–1.54, $p = 0.0034$) and composite CVD events (adjusted HR = 1.24, 95%CI: 1.12–1.38, $p < 0.0001$).

Conclusions: Among men with clinically localized prostate cancer not receiving curative intent therapy, we found increased risk of non-fatal cardiovascular disease with primary ADT use as mono-therapy.

567. Risk of Fracture Following Bisphosphonate Drug Holiday

Jennifer L. Kuntz,[1] John L. Adams,[2] Marsha A. Raebel,[3] Beth T. Tang,[4] Vinutha Vijayadeva,[5] Elizabeth A. McGlynn,[2] Wendolyn S. Gozansky,[3] Annette L. Adams.[4] *[1]Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA; [2]Kaiser Permanente Center for Effectiveness & Safety Research, Pasadena, CA, USA; [3]Kaiser Permanente Colorado Institute for Health Research, Denver, CO, USA; [4]Kaiser Permanente Southern California Department of Research and Evaluation, Pasadena, CA, USA; [5]Kaiser Permanente Hawaii Center for Health Research, Honolulu, HI, USA.*

Background: Bisphosphonate (BP) use to manage osteoporosis and prevent fracture is common; however, recent reports of fractures associated with long-term use have led clinicians and patients to consider BP drug holidays.

Objectives: The aim of this study was to compare the incidence of osteoporosis-related fragility fractures among women with persistent BP use with the incidence among women who took a drug holiday, defined as discontinuation of BPs for at least 12 months.

Methods: We conducted a retrospective cohort study among women aged ≥45 years from four Kaiser Permanente (KP) regions who initiated BP use between 01/01/1998 and 31/12/2009. After women accumulated 3 years of BP exposure, they entered our cohort and were then categorized as taking a drug holiday, defined as ≥12 months with 0% adherence, or having persistent use, defined as BP use at ≥50% adherence. We followed drug holiday subjects and persistent users until the first occurrence of an osteoporosis-related fragility fracture. We compared persistent users and drug holiday subjects with regard to demographic and clinical characteristics. Time-varying Cox proportional hazards models were used to compare osteoporosis-related fracture incidence between the two groups.

Results: We observed 28 620 women for a total of 111 997 person-years. Within this cohort, 59.8% of women were persistent BP users ($n = 17\,123$), while 11 497 women (40.2%) were drug holiday subjects. Women who took a drug holiday had fewer comorbidities, higher baseline T-scores, and lower fracture and fall risk scores. We observed 3571 osteoporosis-related fractures. The unadjusted rate ratio (RR) for any osteoporosis-related fractures for drug holiday compared to persistent use was 0.87 (95%CI: 0.81–0.94); the RR for hip fractures only was 1.0 (95%CI: 0.9–1.2). After adjustment for baseline fall and fracture risk, comorbidities, and other bone-active medication use, there was no difference in any fracture risk (hazard ratio (HR) 0.90, 95%CI: 0.80–1.00) or hip fracture risk (HR: 0.84, 95%CI: 0.68–1.03).

Conclusions: Women who undertake a holiday from BP use are not at greater risk of osteoporosis-related fragility fractures, nor hip fractures specifically, than are women who continue to use BPs persistently.

568. Type II Diabetes Mellitus, Antidiabetic Drugs, and Statins and the Risk of Developing Osteoarthritis in Non-weight Bearing Joints

Noel Frey,[1,2] Julia Spoendlin,[1,2] Thomas Huegle,[3] Susan S. Jick,[4] Christoph R. Meier.[1,2,4] *[1]Clinical Pharmacy and Epidemiology, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Othopaedics Clinic, University Hospital Basel, Basel, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Boston University, Lexington, MA, USA.*

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Background: Growing evidence suggests a link between osteoarthritis (OA, mainly in non-weight bearing joints) and the metabolic syndrome (type 2 diabetes mellitus [T2DM] in particular). A positive effect of statins on OA has previously been postulated. Previous results are contradictory due to heterogenic outcome definitions (not focusing on non-weight bearing joints). We are not aware of any studies that examined the association of antidiabetic drugs (ADDs) or statins and OA in non-weight bearing joints only.

Objectives: The aim of this study was to analyse the association between T2DM, ADDs, and statins and the risk of incident OA in hands or fingers.

Methods: We conducted a matched case–control analysis (matched 1:1 on age, sex, GP, history on database, calendar time and BMI) using the Clinical Practice Research Datalink. We included cases with an incident diagnosis of hand/finger OA between 1995 and 2014 and compared the prevalence of T2DM prior to the index date between cases and controls, stratified by disease severity (HbA1C), disease duration and cardiovascular comorbidities, as well as by exposure to ADDs (metformin, sulfonylurea and insulin) and statins sub-stratified by timing (last prescription $</\geq$180 days prior index date) and duration (number of prescriptions) of drug use.

Results: We identified 6928 patients with OA in hand or finger joints, of which 632 were previously diagnosed with T2DM. T2DM was not associated with an altered relative risk estimate of developing OA in hands or fingers overall (OR: 0.95, 95%CI: 0.84–1.08), as well as when stratified by T2DM duration and severity. Increasing ORs with increasing BMI and with additional metabolic comorbidities (OR: 1.53, 95%CI: 0.95–2.48, BMI >27 with T2DM and hyperlipidaemia) were observed. Exposure to ADDs and statins did not influence the ORs for hand/finger OA.

Conclusions: Our study provides evidence that T2DM is not an independent risk factor for OA in non-weight bearing joints. However, interplay of different metabolic conditions within the metabolic syndrome may favour the development of OA. Our results further suggest that the development of incident hand/finger OA is not influenced by ADDs and statins.

569. Comparative Risk of Venous Thromboembolism among Elderly Users of Antipsychotic Drugs

Niklas Schmedt,[1] Bianca Kollhorst,[1] Kathrin Jobski,[1] Tania Schink,[1] Edeltraut Garbe.[1] [1]*Leibniz Institute for Prevention Research and Epidemiology—BIPS GmbH, Bremen, Germany.*

Background: Antipsychotic drugs (APs) have been associated with an increased risk of venous thromboembolism (VTE) in elderly patients, but data on the comparative safety of APs are lacking.

Objectives: This study aimed to investigate the comparative risk of VTE in elderly users of APs.

Methods: We conducted a retrospective cohort study among new users of APs aged ≥65 years in the German Pharmacoepidemiological Research Database (GePaRD) between 2005 and 2011. Patients entered the cohort at the day of their first AP dispensation. Exposure status was based on the AP leading to cohort entry. The outcome was defined as first hospitalization for VTE. All patients were followed until the occurrence of VTE, 180 days after cohort entry, or end of insurance period (incl. death). Multivariable Cox regression was used to estimate confounder adjusted hazard ratios (aHR) of VTE for conventional compared to atypical APs and for 19 individual APs (ref.: risperidone). Stratified estimates were obtained by sex and by the presence of dementia. In sensitivity analyses, patients with a history of VTE were excluded, and the maximum follow-up was varied.

Results: Overall, the cohort comprised 309 273 new AP users. The median age at cohort entry was 78 years, and 68% were female. No statistically significant differential risk of VTE was found between conventional and atypical AP users (aHR: 0.98; 95%CI: 0.91–1.05). Compared to risperidone, statistically significant lower risks were observed for melperone (0.76; 0.64–0.89), quetiapine (0.75; 0.58–0.97), prothipendyl (0.59; 0.36–0.97), promethazine (0.52; 0.43–0.63), fluspirilene (0.42; 0.32–0.54), and sulpiride (0.41; 0.32–0.52). In patients with dementia, a decreased risk of VTE was observed for users of conventional APs compared to atypical APs (0.80; 0.68–0.95) but not in patients without dementia (1.03; 0.88–1.20). No meaningful differences were observed after stratification by sex or with variation of follow-up.

Conclusions: Our study suggests that the risk of VTE does not differ between conventional and atypical APs overall but may be higher in users of atypical APs with dementia. Selected individual APs may be associated with a lower risk compared to risperidone.

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570. Antidepressant Medication Use and Its Association with Cardiovascular Disease

Richard A. Hansen,[1] Yulia Khodneva,[2] Stephen Glasser,[2] Jingjing Qian,[1] Nicole Redmond,[2] Monika M. Safford.[2] *[1]Health Outcomes Research and Policy, Auburn University Harrison School of Pharmacy, Auburn, AL, USA; [2]Division of Preventive Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA.*

Background: Mixed evidence suggests that second-generation antidepressants may increase risk of cardiovascular and cerebrovascular events.

Objectives: This study aimed to assess whether second-generation antidepressant use is associated with acute coronary heart disease (CHD), stroke, cardiovascular disease (CVD) death, and all-cause mortality.

Methods: Secondary analyses were conducted of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) longitudinal cohort study. Second-generation antidepressant use was measured during the baseline (~2003) in-home visit. Outcomes were assessed by telephone every 6 months and adjudicated by medical record review. Cox proportional hazards time-to-event analysis followed participants until their first event on or before 31 December 2011. Hazard ratios were compared across models that adjusted for sociodemographics (model 1), cardiovascular risk factors (model 2), and physical and behavioral risk factors (model 3). Sensitivity analyses considered baseline CVD and shorter follow-up intervals.

Results: Of the 29 616 participants eligible for analysis, 3458 (11.7%) used an antidepressant at baseline. Models adjusting for sociodemographic and cardiovascular risk factors showed an increased risk of acute CHD (HR = 1.21; 95%CI: 1.04–1.41), stroke (HR = 1.27; 95%CI: 1.01–1.59), CVD death (HR = 1.29; 95%CI: 1.09–1.52), and all-cause mortality (HR = 1.27; 95%CI: 1.15–1.40) for antidepressant users. When physical and behavioral risk factors were added to the model, antidepressant use only was associated with increased risk of all-cause mortality (HR = 1.12; 95%CI: 1.01–1.24). Stratified analyses found an increased risk of stroke in antidepressant users that had baseline CVD (HR = 1.37; 95%CI: 1.00–1.88). Models censoring follow-up time at 2 years found an increased risk of all-cause mortality with antidepressants (HR = 1.37; 95%CI: 1.11–1.68).

Conclusions: In fully adjusted models, we observed a marginally significant increase in risk of all-cause mortality with second-generation antidepressants, and this risk was highest over shorter observation periods. Antidepressant-related risk of other outcomes appeared to be mediated by physical and mental health as well as medication adherence.

571. Transient Risk of Breakthrough Seizures Associated with Phenytoin Refilling

Mengdong He,[1] Jodi Segal.[1] *[1]Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.*

Background: Generic substitution is prevalent in the USA; however, clinicians and patients remain wary of use of generic products for drugs with narrow therapeutic indices. Epileptic seizure control is an example of a condition that requires consistent blood concentrations of medications; this cannot be assured when patients switch among medications from different manufacturers and even between product lots.

Objectives: We aimed to quantify the transient risk of seizure activity attributable to refills of phenytoin.

Methods: We conducted a case-crossover study using administrative claims from the Truven Health Analytics: Marketscan Commercial Claims and Encounters database from 2010 to 2012. We required patients to have at least 6 months of constant enrolment in their insurance plan and at least two dispensings of phenytoin as monotherapy for epilepsy. We then identified individuals who had at least one emergency room visit or hospitalization with a primary claim for epilepsy or seizure. The case period was defined as 7 days prior to the index date (first emergency room visit or hospitalization) and control period as 7 days prior to the case period. We used conditional logistic regression to estimate the odds ratio for the discordant individuals who had a refill in one period and not in the other.

Results: We identified 849 individuals meeting our case definition. They were 75% males, and the mean age was 42 years [standard deviation (SD) 14]. Patients refilling phenytoin, with or without switching between manufacturers, had a 16% higher odds [odds ratio (OR) 1.16; 95% confidence interval (CI) 0.75–1.78] of seizure-related emergency room visits or hospitalization when the prescription was refilled in the 7 days prior to the index date.

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Conclusions: Our results suggest, although do not prove, that the period after refill may be a high-risk period for individuals with epilepsy. This has implications for patient safety and suggests that further attention to the pharmacodynamics of this drug across manufacturers may be warranted.

572. Benzodiazepine Use Is Not Associated with an Increased Risk of Alzheimer's Disease or Vascular Dementia

Patrick Imfeld,[1,2] Michael Bodmer,[1,3] Susan S. Jick,[4] Christoph R. Meier.[1,2,4] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Division of General Internal Medicine, University Hospital Bern, Inselspital, Bern, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA.*

Background: Previous observational studies have associated long-term benzodiazepine use with an increased risk of dementia. Limitations in the study methods, however, leave questions about the interpretation of the findings. Additionally, there is only limited and inconsistent information on the association between benzodiazepine use and the risk of specific dementia subtypes, such as Alzheimer's disease (AD) or vascular dementia (VD).

Objectives: The aim was to study the association between benzodiazepine use and the risk of developing AD or VD addressing limitations of previous work.

Methods: We conducted a case–control analysis using the Clinical Practice Research Datalink. We identified patients aged ≥65 years with newly diagnosed AD or VD between 1998 and 2013 and matched them 1:1 to dementia-free controls on age, sex, calendar time, general practice, and number of years of recorded history in the database. We assessed exposure to benzodiazepines prior to the index date and compared to non-use, stratified by number of prescriptions and by type of benzodiazepine received. We used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of developing AD or VD in relation to previous benzodiazepine use by duration and benzodiazepine type and adjusted for body mass index, smoking status, and use of antidepressants or antipsychotics in the model.

Results: We identified 16 823 patients with AD, 9636 with VD, and the same number of matched controls. Benzodiazepine use was not associated with an increased risk of AD. On the contrary, long-term users were at a lower risk of developing AD compared to non-users, a finding that was most pronounced in users of classical benzodiazepines with ≥150 prescriptions (adjusted OR: 0.58, 95%CI: 0.45–0.74). Benzodiazepine use was also not associated with an increased risk of VD, but in contrast to the association with AD, long-term users did not have a reduced risk of VD compared to non-users; the adjusted OR (95%CI) for users with ≥150 prescriptions was 0.89 (0.68–1.16).

Conclusions: Use of benzodiazepines was not associated with an increased risk of developing AD or VD.

573. Association of Antipsychotic Use with Extrapyramidal Symptoms: Data Mining of the Japanese National Receipt Database

Kouichi Hosomi.[1] *[1]Kinki University, Higashiosaka, Japan.*

Background: Atypical antipsychotics are less likely to cause extrapyramidal symptoms (EPS) versus typical antipsychotics. However, recent studies have suggested that both atypical and typical antipsychotics produce a similar risk for EPS.

Objectives: To examine the association between antipsychotic use and EPS risk, we performed data mining using the Japanese national receipt database.

Methods: Sequence symmetry analysis was performed to identify the risk of EPS after antipsychotic use during the period of January 2010 to December 2012. Antipsychotic use in combination with antiparkinsonian drugs was examined by prescription sequence symmetry analysis (PSSA). In this study, antiparkinsonian drugs with anticholinergic action were used as a marker of EPS. Likewise, event sequence symmetry analysis (ESSA) was undertaken to evaluate the association between antipsychotic use and EPS diagnosis. Adjusted sequence ratios (ASRs) with 95% confidence intervals (CI) were calculated.

Results: According to PSSA, significant associations with antiparkinsonian were found for the whole class of antipsychotics and atypical antipsychotics with ASRs of 4.82 (95%CI: 4.74–4.91) and 2.97 (95%CI: 2.93–3.01), respectively, at an interval of 12 months.

A significant association between typical antipsychotic use and antiparkinsonian use was not found. With ESSA, significant associations with EPS were found for the whole class of antipsychotics and atypical antipsychotics with ASRs of 1.67 (95%CI: 1.65–1.69) and 1.49 (95%CI: 1.47–1.50), respectively, at a 12-month interval. A significant association between typical antipsychotic use and EPS was not found. The number of patients who had atypical antipsychotics prescribed first was 1.5 times larger than the number of patients who had typical antipsychotics initially prescribed.

Conclusions: Analysis of the Japanese national receipt database demonstrated that antipsychotic use increases the risk of EPS. Significant associations between EPS and atypical (but not typical) antipsychotic use were found. This finding may be attributed to the prescribing sequence of antipsychotics.

574. Risk Evaluation of Drug-induced Parkinsonism Associated with Antipsychotics Based on Two Different Study Designs

Chieko Ishiguro,[1] Kazuhiro Kajiyama,[1] Yoshiaki Uyama,[1] Emiko Kondo.[1] *[1]Office of Safety I, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan.*

Background: Drug-induced parkinsonism (DIP) is one of the common adverse effects of antipsychotics. However, there are few attempts to assess a quantitative risk in Japan.

Objectives: The aim of this study was to evaluate a risk of DIP in patients treated with antipsychotics through two study designs using health insurance claims data in Japan.

Methods: Design: Using the Japan Medical Data Center claims database (2005–2008), we conducted a sequence symmetry analysis (SSA) and a nested case–control study (NCCS). In the NCCS, 10 control patients were selected for each case from the cohort matched for age and sex.

Setting: In the SSA, a first diagnosis of DIP and a first prescription for any antipsychotics in patients were identified as monthly data. Among 5965 patients prescribed with antipsychotics, 132 received a diagnosis of DIP during the risk period defined as 3 months. In the NCCS, a cohort of 3104 patients prescribed with antipsychotics was identified. Of those, 127 patients were selected as cases of DIP, and 1270 patients were selected as controls.

Exposure: Exposure was defined as a prescription for any typical and atypical antipsychotics in both study designs.

Main outcome measures: DIP occurrence was defined as a diagnosis according to ICD-10.

Statistical analysis: By assessing the distribution of medication–occurrence pairs, a risk of DIP was calculated as adjusted sequence ratio (ASR) in the SSA. In addition, adjusted odds ratio was calculated by conditional logistic regression in the NCCS.

Results: The use of antipsychotics was associated with an increased risk of DIP both in the SSA (ASR, 6.65; 95% confidence interval [CI], 3.93–12.03) and in the NCCS (adjusted odds ratio, 7.67; 95%CI, 4.88–12.0).

Conclusions: This study showed that Japanese patients treated with antipsychotics had nearly a sevenfold increased risk of DIP. The risk of DIP was similar in two different study designs.

575. Risk of Seizures Associated with Antipsychotic Drug Use—A Nested Case–Control Analysis

Marlene Bloechliger,[1] Stephan Rueegg,[2] Susan S. Jick,[3] Christoph R. Meier,[1,3,4] Michael Bodmer.[1,5] *[1]Pharmaceutical Sciences, Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, University of Basel, Basel, Switzerland; [2]Neurology, Division of Clinical Neurophysiology, University Hospital Basel, Basel, Switzerland; [3]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Boston, MA, USA; [4]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [5]General Internal Medicine, University Hospital Bern, Inselspital, Bern, Switzerland.*

Background: Limited data from clinical trials, case reports, and analyses of pharmacovigilance databases have reported an association between the use of antipsychotics and the development of seizures. Low-potency first-generation antipsychotics and clozapine, olanzapine, and quetiapine have been associated with a higher risk of inducing seizures than high-potency first-generation or other second-generation antipsychotics. No data from observational studies are available in the current literature.

Objectives: This study aimed to investigate the risk of first-time seizures associated with antipsychotic use in patients with psychiatric disorders.

Methods: We conducted a retrospective follow-up study with a nested case–control analysis between January 1998 and December 2013 using data from the UK-based Clinical Practice Research Datalink. We estimated incidence rates in patients with dementia, affective disorders, or schizophrenia, who used high or low-potency first-generation antipsychotics, olanzapine or quetiapine, other second-generation antipsychotics, or no antipsychotics. To adjust for potential confounding, we estimated odds ratios of antipsychotic drug use among cases with seizures and matched controls in a nested case–control analysis.

Results: Of 60 131 patients with psychiatric disorders, 571 developed an incident seizure during follow-up. Incidence rates per 10 000 person-years were higher in antipsychotic users (38.0 [95%CI, 31.1–44.9]) than non-users (11.7 [95%CI, 10.0–13.4]). Current users of low-potency and high-potency first-generation antipsychotics were at an increased risk of seizures compared with non-users (adjusted odds ratios 1.66 [95% CI: 0.94–2.95] and 2.34 [95%CI: 1.57–3.49]), while current users of olanzapine or quetiapine and other second-generation antipsychotics (adjusted odds ratios 1.23 [95%CI: 0.83–1.82] and 0.59 [95%CI: 0.36–0.95]) were not.

Conclusions: Current use of low-potency and high-potency first-generation antipsychotics was associated with a twofold increased risk of developing seizures compared with non-use of antipsychotics.

576. Comparative Risk of Death Among Elderly Users of Antipsychotic Drugs

Niklas Schmedt,[1] Bianca Kollhorst,[1] Kathrin Jobski,[1] Tania Schink,[1] Edeltraut Garbe.[1] *[1]Leibniz Institute for Prevention Research and Epidemiology—BIPS GmbH, Bremen, Germany.*

Background: Antipsychotic drugs (APs) have been associated with an increased risk of death in elderly patients, but data on the safety of individual APs are scarce.

Objectives: The aim of this study was to investigate the comparative risk of death in elderly users of APs.

Methods: We conducted a retrospective cohort study among new users of APs aged ≥65 years in the German Pharmacoepidemiological Research Database (GePaRD) between 2005 and 2011. Patients entered the cohort at the day of their first AP dispensation. Exposure status was based on the AP leading to cohort entry. Patients were followed until death, 180 days after cohort entry or end of insurance. Multivariable Cox regression was used to estimate confounder adjusted hazard ratios (aHR) of death for conventional compared to atypical APs and for 19 individual APs (ref.: risperidone). In an additional analysis of conventional versus atypical APs, propensity-score (PS) adjustment was used. Stratified estimates were obtained by sex and for AP users with and without dementia. In sensitivity analyses, patients with a history of cancer were excluded, and the maximum follow-up was varied.

Results: Overall, the cohort comprised 309 273 new AP users. Median age at cohort entry was 78 years, and 68% were female. Use of conventional APs increased the risk of death compared to atypical APs (aHR: 1.53; 95%CI: 1.49–1.57). PS adjustment did not change these results. On a substance basis, levomepromazine (1.69; 1.59–1.80), haloperidol (1.62; 1.56–1.68), zuclopenthixol (1.28; 1.08–1.51) and melperone (1.10; 1.06–1.13) were associated with an increased risk. For all other APs except pipamperone, amisulpride and aripiprazole, a lower risk compared to risperidone was found. Patients without dementia had a higher aHR compared to patients with dementia (1.77; 1.70–1.84 vs 1.27; 1.23–1.32). Males were at slightly higher risk of death than females. Excluding cancer patients diminished the aHR of death for conventional APs to 1.29 (1.25–1.33). An increasing risk of death was observed with shorter maximum follow-up.

Conclusions: Our results indicate an increased risk of death for elderly users of conventional compared to atypical APs and a large heterogeneity in the safety profiles of individual APs.

577. All-cause Mortality among Elderly Users of Antidepressant Drugs in Germany

Bianca Kollhorst,[1] Kathrin Jobski,[2] Niklas Schmedt,[2] Tania Schink,[2] Edeltraut Garbe.[2] *[1]Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany; [2]Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology—BIPS, Bremen, Germany.*

Background: Antidepressant drugs (ADs) have been associated with an increased mortality in elderly patients, but data on the safety of individual ADs are still scarce.

Objectives: The aim of this study was to compare all-cause mortality of elderly users of tricyclic and tetracyclic ADs (TCA), selective serotonin reuptake (SSRI), monoamine oxidase (MAO), selective serotonin noradrenalin reuptake (SSNRI) and noradrenalin reuptake inhibitors (NARI), other ADs and individual ADs.

Methods: We conducted a cohort study among new users of ADs aged 65 years and older in the German Pharmacoepidemiological Research Database (2005–2011). Patients entered the cohort at their first AD dispensation and were followed until the first of the following events: death, 180 days after cohort entry, end of insurance or a dispensation of an antipsychotic drug. Cox models were used to estimate adjusted hazard ratios (HR) and confidence intervals (CI) for mortality risk. Subgroup analyses were conducted based on sex and depression. In sensitivity analyses, patients with a history of cancer were excluded, and the maximum follow-up was varied.

Results: The cohort comprised 439 317 new AD users (median age of 72 years, 72% female). Compared to TCAs, SSRIs and MAO inhibitors showed an increased mortality risk (HR: 1.18; 95%CI: 1.14–1.22 and HR: 1.27; 95%CI: 1.02–1.59), whereas decreased risks were observed for SSNRIs (0.78; 0.72–0.86) and other ADs (0.63; 0.57–0.71). Several individual drugs revealed a decreased mortality risk compared to citalopram including opipramol (0.58; 0.54–0.62), trimipramine (0.67; 0.63–0.72), duloxetine (0.49; 0.43–0.56) and hypericum (0.48; 0.42–0.55). Estimates of SSRIs differed significantly in males and females (1.08; 1.02–1.14 vs 1.26; 1.20–1.31). Only in SSNRI users, risks differed in patients with and without depression (0.85; 0.57–0.75 and 0.73; 0.65–0.83). Shorter maximum follow-up decreased the risk of mortality for SSRIs and other ADs. Excluding patients with cancer increased the estimates for SSRIs, SSNRIs and MAO inhibitors.

Conclusions: Our results indicate an increased risk of mortality for elderly users of SSRIs and MAO inhibitors versus TCAs. In the safety of individual ADs, considerable differences were found.

578. Use of Antipsychotics and the Risk of Fracture: A Systematic Review and Meta-analysis of Observational Studies

Wan-Ting Hsu,[1] Jason Wang,[2] Yi-Han Sheu,[3] Che-Wei Su,[4] Sheng-Chi Tung,[5] Chien-Chang Lee.[3,6]

[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Paul L. Foster School of Medicine, Texas Tech University, El Paso, TX, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [4]Mackay Medical College, New Taipei City, Taiwan; [5]Department of Anesthesiology, Cathay General Hospital, Taipei, Taiwan; [6]Department of Emergency Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan.

Background: There have been concerns that chronic use of antipsychotics is associated with an increased risk for fractures. It has been postulated that the use of these drugs may lead to an increased tendency to fall as a result of orthostatic hypotension or sedation.

Objectives: To further explore this, we performed a systematic review and meta-analysis of controlled observational studies to evaluate the risks of antipsychotics use on fracture outcome.

Methods: A comprehensive search was conducted in the Medline, EMBASE, and Scopus from inception through December 2014. All observational studies that compared fracture outcome in antipsychotic patients with a control group were included. Three reviewers extracted data and evaluated bias using the Newcastle–Ottawa Scale. Random or fixed effects models were used to calculate pooled odd ratios and evaluate heterogeneity (I^2).

Results: Of 162 identified studies, 12 studies (four cohort and eight case–control) with 66 537 fracture cases were included in our analysis. Compared with nonusers, both conventional and atypical antipsychotic users were at significantly higher risk for hip or femoral fractures, with a pooled odds ratio of 1.55 (95%CI, 1.35–1.77; $I^2 = 58\%$) and 1.38 (95%CI, 1.10–1.72; $I^2 = 56\%$), respectively. In the subgroup analysis, this association was observed in both elderly and adult patients. We estimated studies provided data on individual agents and found that patients taking chlorpromazine were at the highest risk for fracture (odds ratio 2.01; 95%CI, 1.43–2.83; $I^2 = 55.3\%$), while patients taking risperidone were at a lower risk of fracture (odds ratio 1.29; 95%CI, 0.89–1.85; $I^2 = 55.3\%$). There was a significant statistical and clinical heterogeneity among the studies for the main analysis and most of the subgroup analyses.

Conclusions: In pooling observational studies of almost 430 000 patients, antipsychotics use was

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associated with a significant relative increase in hip fractures compared with patients who were not taking antipsychotics. Nevertheless, our results should be interpreted in the context of the inherent limitation of observational studies.

579. Risk of Medication Use for Heat-related Hospital Admissions—A Matched Case–Control Study

Ying Zhang,[1] Monika Nitschke,[2] Antoinette Krackowizer,[3] Peng Bi.[3] *[1]School of Public Health, University of Sydney, Sydney, Australia; [2]Dept. of Health, South Australian Government, Adelaide, Australia; [3]School of Population Health, University of Adelaide, Adelaide, Australia.*

Background: Previous studies show that certain medicines may be related to a higher risk of morbidity during heat waves, but quantitative evidences are very limited.

Objectives: The aim of this study was to examine if medication use can increase the risk of heat-related hospitalization.

Methods: A matched case–control study was conducted in metropolitan Adelaide, South Australia. Cases were those who had hospital admissions with heat-related diagnoses based on selected ICD codes during the 5-day heat wave exposure period in 2009. Controls were matched with cases on age (±2 years) and gender and randomly selected from communities using the electoral database. Cases and controls were interviewed face-to-face or by telephone to collect data on demographics, living environment, social support, health status, behavior change and medication use during the heat wave. Descriptive analyses and simple and multiple conditional logistic regressions were performed.

Results: In total, 143 patients and 143 matched community controls were interviewed, with a mean age of 73 years (SD: 21). Compared with controls, cases had a significantly higher prevalence of using medications for heart diseases (38% vs 20%, $p < 0.01$), depression (40% vs 18%, $p < 0.01$), diabetes (23% vs 11%, $p < 0.05$) and antibiotics (17% vs 14%, $p < 0.05$). After controlling for confounders including co-morbidities, social and individual factors, the multiple regression models showed that cases were more likely to use medication for depression (adjusted OR = 7.35, 95%CI: 1.13–47.62) but not for the other medicines.

Conclusions: Our study indicates that medication use for depression could significantly increase the risk of heat-related morbidity during heat waves, which should be considered in improving clinical guidelines and interventions to reduce heat-related morbidity in a warming climate.

580. Use of Antipsychotics and the Risk of Pneumonia: A Systematic Review and Meta-analysis of Observational Studies

Chien-Chang Lee,[1,2] Wan-Ting Hsu,[3] John W. Jackson,[1] Jason Wang,[4] Albert Yuh-Chyuan Shan,[5] Wei Kian Chua.[6] *[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; [2]Department of Emergency Medicine, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan; [3]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Paul L. Foster School of Medicine, Texas Tech University, El Paso, TX, USA; [5]Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan; [6]Department of Pediatrics, Buddhist Tzu Chi General Hospital, Hualien, Taiwan.*

Background: A number of large population-based epidemiological studies have observed an association between the use of antipsychotics and an increased risk for pneumonia.

Objectives: We aimed to perform a systematic review and meta-analysis of conventional and atypical antipsychotics in relation to the risk of either community-acquired or hospital-acquired pneumonia.

Methods: We searched Medline and EMBASE from inception through December 2014 for cohort or case–control studies that evaluated the association between use of antipsychotics and risk of pneumonia. We used fixed or random effect models to calculate the weighted summary odds ratio (OR). Tests for heterogeneity and publication bias were also performed.

Results: We identified six eligible studies with a total of 119 577 subjects and 3794 cases of pneumonia. Conventional antipsychotics were associated with a significantly increased risk of pneumonia [OR: 1.61; 95%CI: 1.28–2.02; $I^2 = 64.3\%$]. Atypical antipsychotics were associated with an even higher risk of pneumonia [OR: 2.12; 95%CI: 1.69–2.64; $I^2 = 46.9\%$]. Subgroup analysis of atypical antipsychotics showed that elderly patients were at higher risk

for pneumonia [OR: 2.70; 95%CI: 1.97–3.71; $I^2 = 0\%$], as compared to young adult patients.

Conclusions: Use of antipsychotics, especially current users of atypical antipsychotics, appears to be associated with an increased risk for developing pneumonia. Elderly individuals taking atypical antipsychotics experienced a highest risk of pneumonia. Given the inevitable limitations of observational studies for reliably ascertaining relative risks as small as the ones identified here, future sufficiently powered randomized controlled trials are needed to validate our findings.

581. Comparative Safety of Typical and Atypical Antipsychotics after Cardiac Surgery

Dae Kim,[1,2] Elisabetta Patorno,[1] Yoonyoung Park,[1,3] Krista Huybrechts,[1] Raisa Levin,[1] Brian Bateman.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; [2]Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: Typical and atypical antipsychotic agents are often used to reduce symptoms of delirium after cardiac surgery, but their comparative safety remains uncertain.

Objectives: This study aimed to determine the risk of in-hospital mortality and safety events associated with atypical versus typical antipsychotic use after cardiac surgery.

Methods: We conducted a retrospective cohort study using the Premier research database (2003–2011) that included 11 869 adults who initiated an antipsychotic agent after coronary artery bypass grafting or valve surgery. We created two propensity score (PS)-matched new-user cohorts to compare either oral atypical antispychotics ($n = 1626$) or intravenous typical antipsychotics ($n = 2250$) to oral typical antipsychotics. In the PS-matched cohorts, we compared the incidence of in-hospital mortality and other safety outcomes, including suspected cardiac arrhythmia, pneumonia, and use of brain imaging that were identified using appropriate codes following antipsychotic initiation.

Results: In the PS-matched cohorts, there was statistically non-significant trend for a modest increase in in-hospital mortality with oral atypical antipsychotics (6.6% vs 5.3%; odds ratio [OR]: 1.27; 95% confidence interval [CI]: 0.84–1.93) and intravenous typical antipsychotics (6.6% vs 4.9%; OR: 1.37; 95%CI: 0.96–1.96) compared with oral typical antipsychotics. After PS matching, suspected pneumonia and use of brain imaging were more common with oral atypical antipsychotics (29.3% vs 22.3% for pneumonia and 17.7% vs 12.3% for brain imaging) and intravenous typical antipsychotics (36.7% vs 20.1% and 19.7% vs 12.3%, respectively) than oral typical antipsychotics ($p < 0.05$). Suspected cardiac arrhythmia was similar for oral atypical antipsychotics (2.0% vs 2.0%) and intravenous typical antipsychotics (2.3% vs 2.0%) compared with oral typical antipsychotics.

Conclusions: The use of oral atypical and intravenous typical antipsychotics may be associated with higher risks of suspected pneumonia and use of brain imaging and possibly modest increase in in-hospital mortality compared with oral typical antipsychotics after cardiac surgery.

582. Observational Assessment of Safety in Seroquel (OASIS)—Rates and Patterns of Common Events Observed in Users of Quetiapine Extended Release (Seroquel XL©) and Immediate Release (IR)

Deborah Layton,[1,2] Sarah Clarke,[1] Ian Ratcliffe,[1] Saad A. W. Shakir,[1,2] Tony Hale.[3] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK; [3]University of Kent, Canturbury, Kent, UK.*

Background: The aim of OASIS (ENCePP Study reg.5412) was to extend the post-authorisation safety knowledge of quetiapine XL, with a focus on short-term (12-week (w)) safety and high-dose (>600 mg/day) use, as prescribed by psychiatrists in patients (pts) with schizophrenia (Schiz) or bipolar disorder (BD), versus quetiapine IR. Study objectives include quantifying event incidence and pattern.

Objectives: The aim of this study was to compare common event rates between users defined by dose and formulation.

Methods: An observational cohort design. Questionnaires completed by specialists collected data on pt characteristics, exposure and events (December 2009

to December 2012). Exposure (pt-w) was calculated for total cohort and stratified by formulation. Stratum-specific exposure was calculated for three 4-w periods for total cohort, formulation and high-dose use (where >600 mg/day for >50% of each 4-w period). Crude event incidence densities (ID) per 1000 pt-w and ID differences (IDD + 95%CI) were calculated within/between groups; IDD 95%CI excluding the null (0) were signals of events associated with starting treatment and/or high dose.

Results: Cohort = 845: Schiz: 338(40%), BD: 442 (52%), other: 65 (8%); 471 (59%) female; median age 39 (IQR 29, 49). High-dose use was reported for 28/631 (4%) in XL group and 3/214 (1%) in IR group. The most frequently reported events (not associated with indication) were sedation : ID 24, somnolence : ID 20, akasthesia : ID 3 and parkinsonism : ID 2. In the XL group, the IDDs for these four events were non-significantly lower for high versus standard dose for total study period and weeks 1–4. Within XL high-dose group, sedation and somnolence were associated with starting treatment (IDD w_{1-4}–w_{5-8}: 25 (7, 42) and 14 (14, 15), respectively); this pattern was also observed within XL and IR standard dose groups. Low counts in high-dose group and IR cohort precluded reliable comparisons.

Conclusions: This study found that sedation and somnolence were common events associated with starting treatment but not with high dose. Although the frequency of high-dose use was low, OASIS provides important information on the safety and utilisation of quetiapine XL.

583. Suicide Risk and Side Effects from Antipsychotics in Schizophrenia: A Nested Case–Control Study

Johan Reutfors,[1] Shahram Bahmanyar,[1] Lena Brandt,[1] Eric Clapham,[2] Erik G. Jönsson,[3] Robert Bodén,[1,2] Anders Ekbom,[1] Urban Ösby.[4] *[1]Department of Medicine, Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden; [2]Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden; [3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [4]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden.*

Background: A higher risk of suicide is well documented in schizophrenia, but the potential relationship with medication side effects is not well understood.

Objectives: This study aimed to explore suicide risk in schizophrenia in relation to side effects from antipsychotic medication.

Methods: Among all patients with a first clinical discharge diagnosis of schizophrenia or schizoaffective disorder in Stockholm County between 1984 and 2000 ($n = 4000$), those who died by suicide within 5 years from diagnosis were defined as cases ($n = 84$; 54% male). For each case, one individually matched control was identified from the same population. Information on symptoms of antipsychotic side effects as well as prescriptions of anticholinergic medication was retrieved from clinical records in a blinded fashion. Adjusted odds ratios [OR] with 95% confidence intervals [CI] of the association between suicide and side effects as well as anticholinergic medication were calculated by multivariate conditional logistic regression.

Results: A lower suicide risk was found in patients with extrapyramidal side effects (OR: 0.33, 95%CI: 0.12–0.94). Patients with a history of use of anticholinergic drugs had a non-significant lower suicide risk (OR: 0.77, 95%CI: 0.33–1.80). Akathisia was studied separately and did not affect the suicide risk significantly (OR: 1.21, 95%CI: 0.44–3.33).

Conclusions: Extrapyramidal side effects (except akathisia) may be associated with a lower suicide risk in the early phase of schizophrenia. This could reflect higher adherence to antipsychotic medication among these patients.

584. The Potential Risk of Upper Gastrointestinal Bleeding Associated with Use of Selective Serotonin Reuptake Inhibitors in Older Adults

Eunsun Noh,[1] Brian J. Quilliam.[1] *[1]College of Pharmacy, University of Rhode Island, Kingston, RI, USA.*

Background: Selective serotonin reuptake inhibitors (SSRIs) are recommended as a first-line therapy for depression in older adults because of their favorable adverse event profile; however, several observational studies have suggested an increased risk of gastrointestinal (GI) bleeding associated with SSRIs. While this potential link remains controversial, it is important to evaluate the risk of GI bleeding in association with SSRI use, especially in older adults who take multiple medications that may increase the risk of GI bleeding.

Objectives: The aim of this study was to quantify the effects of SSRI use on upper GI bleeding in older Medicare beneficiaries.

Methods: We performed a nested case–control study using the Medicare Current Beneficiary Survey data from 2006 to 2008. Cases included all older adults (≥65 years) diagnosed with upper GI bleeding. Using incidence density sampling, we randomly selected up to six controls who had no evidence of upper GI bleeding. We matched cases and controls with regard to age (±5 years), gender, calendar year, and Charlson comorbidity score. We developed a conditional logistic regression model to quantify the risk of upper GI bleeding associated with use of SSRIs, simultaneously adjusting for potential confounders. We further assessed whether use of non-steroidal anti-inflammatory drugs (NSAIDs) modified the effect of SSRI use on upper GI bleeding.

Results: We identified 152 cases and randomly selected 820 matched controls. We observed no significant association between use of SSRIs and an increased risk of upper GI bleeding in older adults (adjusted odds ratio [AOR] = 1.3; 95% confidence interval [CI], 0.7–2.5). Moreover, after adjusting for confounding factors, use of SSRIs along with NSAIDs was not significantly associated with an increased risk of upper GI bleeding (AOR = 1.8; 95%CI, 0.5–6.7).

Conclusions: Our findings did not confirm the effect of SSRIs on an increased risk of upper GI bleeding in older adults. As this study does not provide conclusive data, clinicians must weigh the potential risks including upper GI bleeding when prescribing these medications.

585. Anticholinergic Medication Use and Risk of Community-acquired Pneumonia in Older Adults

Kathleen J. Paul,[1] Rod L. Walker,[2] Sascha Dublin.[2] *[1]Group Health Family Practice Residency, Group Health Cooperative, Seattle, WA, USA; [2]Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA.*

Background: Anticholinergic medications can cause adverse events in older people via mechanisms including confusion and sedation. No prior study has examined their association with pneumonia risk.

Objectives: The aim of this study was to examine whether acute or chronic use of anticholinergic medications is associated with risk of community-acquired pneumonia in older adults.

Methods: We conducted a population-based, nested case–control study within Group Health, an integrated healthcare delivery system in the northwest USA. Among community-dwelling immunocompetent adults aged 65–94 years, we ascertained potential pneumonia cases from 2000 to 2003 using electronic diagnosis data and validated them via chart review ($n = 1039$). Controls ($n = 2022$) were matched 2:1 to cases by age, sex, and year. For cases, the index date was defined as the date of pneumonia diagnosis, with controls assigned the same index date as their matched case. Anticholinergic medication use was ascertained from electronic pharmacy data; acute use was defined as 1+ prescription fills 90 days or less before the index date, past use as 1+ fills in the prior year but none within 90 days, and nonuse as no fills in the prior year. Adults with 3+ fills in the prior year were classified as chronic users. Analyses used conditional logistic regression, adjusting for covariates from medical record review and electronic data including comorbid illnesses and functional and cognitive status.

Results: The most commonly used anticholinergic medication classes were gastrointestinal medications, pain medications, and antidepressants. Nonuse (the referent category) was observed in 24% of cases and 42% of controls. Acute anticholinergic use was seen in 59% of cases and 35% of controls (adjusted OR: 2.55, 95%CI: 2.08–3.13, compared to nonuse) and past use in 17% of cases and 23% of controls (OR: 1.19 [0.92–1.53]). Chronic use was present in 53% of cases and 36% of controls (OR: 2.07 [1.68–2.54]). Results were not different for high-potency and low-potency anticholinergic medications.

Conclusions: In older adults, anticholinergic medication use is associated with pneumonia risk, adding to substantial evidence that these medications are high risk for older adults.

586. Effects of Second-generation Antidepressants on Cognitive Function: A Systematic Review and Meta-analysis

Shalak Gunjal,[1] Satabdi Chatterjee,[1] Helena VonVille,[2] Patricia Dolan Mullen,[2] Hua Chen,[1] Rajender Aparasu.[1] *[1]Department of Pharmaceutical Health Outcomes and Policy, College of Pharmacy, University of Houston, Houston, TX, USA; [2]Division of Health Promotion and Behavioral Sciences, School*

of Public Health, The University of Texas Health Science Center at Houston, Houston, TX, USA.

Background: Second-generation antidepressants (SGADs) are currently the first line of treatment for depression.

Objectives: The aim of this study was to determine the effects of SGADs on cognition through a systematic review and meta-analysis of scientific literature.

Methods: Electronic searches in MEDLINE, PubMed, PsycINFO, CINAHL, and Embase for English-language abstracts from 1980 to 2014 were conducted with following inclusion criteria: population: adults (age $\geq$ 18) with depression; intervention: SGADs available in the USA based on 2014 American Hospital Formulary Service; comparator: placebo or SGADs; outcomes: attention, processing speed, executive function, and memory; and study design: randomized controlled trials and observational studies. The methodological quality of the studies was assessed by Cochrane risk of bias tool. A random effects model was used to estimate the pooled effects of SGAD use on cognition.

Results: A total of 4274 abstracts were screened; 342 were retrieved for a full-text review. Of them, 17 (13 RCTs and four observational) studies involving a total of 2437 depressed patients were included. Studies were of optimum quality as assessed by the risk of bias tool. Mini-mental State Exam (MMSE), Stroop color word test (SCWT), choice reaction time task (CRT), and digit symbol substitution test (DSST) were commonly used cognitive tests. The meta-analysis on studies reporting MMSE found no effect of SGADs on cognition (standardized mean difference (SMD) = 0.126; 95%CI: 0.046, 0.298). Due to insufficient and inconsistent reporting of results involving SCWT, CRT, and DSST, systematic reviews were performed. Findings from the reviews suggest positive impact of SGADs on executive function (using SCWT) and attention and processing speed (using CRT). Mixed evidence existed regarding the impact of SGADs on attention and processing speed using DSST.

Conclusions: The meta-analysis of studies reporting MMSE found no evidence of improved cognition with SGADs. Systematic reviews on studies involving other cognitive tests suggest variable evidence for SGADs effects on specific domains. Future studies involving reliable and widely used cognitive tests are needed to quantify the cognitive impact of SGADs.

587. The Impact of Intravitreal Drugs on Rates of Post-injection Endophthalmitis

Brian L. VanderBeek,[1,2,3] Sarah Bonaffini,[1,4] Liyuan Ma.[3] *[1]Ophthalmology, University of Pennsylvania Scheie Eye Institute, Philadelphia, PA, USA; [2]Center for Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA; [3]Leonard Davis Institute, University of Pennsylvania, Philadelphia, PA, USA; [4]Medical School, Lake Erie College of Osteopathic Medicine, Bradenton, FL, USA.*

Background: Endophthalmitis, a blinding ocular infection, has been associated with compounded bevacizumab (an anti-VEGF agent) used in intravitreal injections, raising relative safety concerns over its in-class comparator, ranibizumab. Steroids are an alternative, but their rate of endophthalmitis has never been compared to anti-VEGF agents.

Objectives: This study aimed to compare post-intravitreal injection endophthalmitis rates: bevacizumab versus ranibizumab and intraocular steroids versus anti-VEGF agents.

Methods: The medical claims from a large, national US insurer were searched for all intravitreal injections (CPT67028) done between 2003 and 2012 for inclusion in this retrospective cohort study. Cohorts were based on anti-VEGF agents (bevacizumab, ranibizumab, aflibercept, and pegaptanib) individually and collectively for comparison with intraocular steroids (triamcinolone and dexamethasone). Cases were defined as having a new endophthalmitis diagnosis (ICD9 360.0x) and a "tap and inject" procedure (CPT67015, 67025) or an intravitreal injection of antibiotics on the same day, 1–14 days of post-injection. Exclusion occurred for any history of endophthalmitis, $<$6 months look-back or $<$1 month follow-up time after injection. The main outcome measures were the odds of endophthalmitis using logistic regression while controlling for injection-associated diagnosis.

Results: Of the 452 762 total injections given to 72 687 patients, 299 000 were bevacizumab, and 87 505 were ranibizumab. Fifty (rate = 0.017%, 1/5980 injections) and 22 (0.025%, 1/3978) cases of endophthalmitis occurred, respectively. No significant difference in endophthalmitis rates between the anti-VEGF agents (OR = 1.54, 95%CI: 0.93, 2.57; $p = 0.095$) was seen. A total of 390 946 anti-VEGF injections and 18 105 steroid injections were performed, which were followed by 74 (0.019%, 1/5283) and 24 (0.13%,

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1/754) cases of endophthalmitis, respectively. The odds of endophthalmitis were 6.90 (95%CI: 3.78, 12.58; $p < 0.001$) times higher post-steroid injection compared to anti-VEGF injections.

Conclusions: The need to compound bevacizumab for intraocular use does not affect the rate of endophthalmitis. Steroid injections were associated with considerably higher odds of endophthalmitis.

588. Low-dose Aspirin, Non-steroidal Anti-inflammatory Drugs, Selective COX-2 Inhibitor Prescriptions and Breast Cancer Recurrence: A Danish Population-based Cohort Study

Deirdre Cronin-Fenton,[1] Uffe Heide-Jørgensen,[1] Thomas P. Ahern,[2] Timothy L. Lash,[1,3] Peer Christiansen,[4,5] Bent Ejlertsen,[5,6] Henrik T. Sørensen.[1] *[1]Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Surgery & Biochemistry, University of Vermont, Burlington, VT, USA; [3]Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA; [4]Surgery P, Aarhus University Hospital, Aarhus, Denmark; [5]Danish Breast Cancer Cooperative Group, Copenhagen, Denmark; [6]Oncology, Rigshospitalet, Copenhagen, Denmark.*

Background: Low-dose aspirin, non-steroidal anti-inflammatory drugs (NSAID), and selective COX-2 inhibitors (sCOX-2i) may improve outcomes in breast cancer patients.

Objectives: The aim of this study was to investigate the association of aspirin, NSAID, and sCOX2i use, with breast cancer recurrence (BCR).

Methods: Incident early-stage breast cancer patients diagnosed 1996–2008 were identified in the Danish Breast Cancer Cooperative Group Registry. Aspirin, NSAIDs, and sCOX2i prescriptions were ascertained from the National Prescription Registry. Follow-up began on the date of breast cancer primary surgery and continued to BCR, death, emigration, or 31/07/2013. We used Cox regression models to compute the HR and corresponding 95%CI associating prescriptions with BCR, adjusting for confounders. We treated the exposure drugs as time-varying exposures lagged by 1 year and lagged by 2 years in sensitivity analyses.

Results: We identified 34 188 patients with 233 130 person-years of follow-up. Median follow-up was 7.1 years; 16% developed BCR. Compared with non-use, use of aspirin, NSAIDs, and sCOX2i did not affect BCR rate (HR adjusted aspirin = 1.0, 95% CI = 0.90, 1.1; NSAIDs = 0.99, 95%CI = 0.92, 1.1; and sCOX2i = 1.1, 95%CI = 0.98, 1.2). Findings remained near null in analyses associating the number of prescriptions with the rate of BCR: analyses restricted to women without a history of prediagnostic exposure drug use, analyses stratified by estrogen receptor status and stage, and in analyses of specific recurrence sites. Pre-diagnostic low-dose aspirin use was not associated with BCR.

Conclusions: This prospective cohort study shows little effect of aspirin, NSAIDs, or sCOX2i prescriptions on breast cancer recurrence.

589. Ethnic and Regional Differences in Neutrophil Counts and Neutropenia Reporting in Two International Clinical Trials of Rifapentine and Rifampicin for Tuberculosis Treatment

Ruth N. Moro,[1,6] John L. Johnson,[2,3] Chi-Chiu Leung,[4] Kwok-Chiu Chang,[4] Neil Martinson,[5] Andrey Borisov,[1] Stefan V. Goldberg.[1] *[1]Division of Tuberculosis Elimination, Clinical Research Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA; [2]Uganda-Case Western Reserve University Research Collaboration, Kampala, Uganda; [3]Case Western Reserve University School of Medicine, Cleveland, OH, USA; [4]Department of Health, Tuberculosis and Chest Service, Hong Kong, China; [5]University of the Witwatersrand and Baragwanath, Soweto, South Africa; [6]CDC Foundation, Atlanta, GA, USA.*

Background: Variation in absolute neutrophil count (ANC) between Africans and other populations has been reported. Standard toxicity tables (STT) are commonly used to assign severity grades to laboratory values in clinical trials (CT) but have not been assessed in different populations. Neutropenia has been associated with rifamycin use.

Objectives: This study aimed to identify possible ethnic and regional variation of ANC at baseline, to identify STT 1 grade 3 adverse events of neutropenia, stratified by race, and to compare the use of STT1 versus STT2 in the reporting of safety data.

Methods: Two CT used rifapentine (P) in place of rifampicin (R) during intensive phase of otherwise standard tuberculosis treatment. Three hundred and thirty-seven participants received R10 mg/kg, and

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three groups of 361, 81, and 81 received P10, P15, and P20 mg/kg, respectively. ANC and clinical manifestations were evaluated at baseline and weeks 2, 4, 6, 8, and 12. Neutropenia grade 3 was defined by STT1 ($<$1000–500/mm^3) or STT2 ($<$600–400/mm^3) and compared between populations.

Results: Eight hundred and sixty participants received at least one dose of study drugs, 590 (69%) were male, and 86 (10%) were HIV infected. Thirty-two (3.7%) neutropenia events (NE) defined by STT1 were reported, all of them in Black participants; one developed fever. Laboratory values improved without treatment interruption. NE rates did not differ by treatment arm or dose. Black participants had lower median ANC baseline values compared to non-Black participants (p-value < 0.001). Among Black participants, those living in Africa had lower baseline median ANC compared to those living in non-African countries (p-value $= 0.004$). Among participants living outside Africa, Blacks had similar baseline median ANC compared to non-Blacks. If STT2 criteria were applied, only four NE would have been reported.

Conclusions: Compared with non-Black participants, Black participants had lower baseline ANC values and a higher frequency of grade 3 neutropenic events using the STT1 scoring system. Consideration of the participant population and the clinical implications of neutropenia might be helpful in optimizing neutropenia reporting definitions for TB CT.

590. The Role of Allopurinol and Febuxostat in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Maja Mockenhaupt,[1] Peggy Sekula,[2] Jean-Claude Roujeau.[3] *[1]Dokumentationszentrum Schwerer Hautreaktionen (dZh), Department of Dermatology, Medical Center—University of Freiburg, Freiburg, Germany; [2]Center for Medical Biometry and Medical Informatics, Medical Center—University of Freiburg, Freiburg, Germany; [3]RegiSCAR-France, University Paris-Est Créteil (UPEC), Creteil, France.*

Background: Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are severe cutaneous adverse reactions reflecting severity variants of the same disorder. Allopurinol, a uric acid-lowering agent, is the drug most frequently associated with SJS/TEN in Europe. Febuxostat was introduced in Europe in 2010 for the same indication.

Objectives: The aim of this study was to assess the number of allopurinol-induced and of febuxostat-induced cases of SJS/TEN in Ile de France and Germany.

Methods: RegiSCAR is an ongoing international registry of patients with SJS/TEN since 2003. Between 2003 and 2011, 856 patients with a confirmed diagnosis of SJS or TEN were included in France and Germany. Case collection is assumed to be complete within Ile de France and Germany. Drug causality for each patient was evaluated using ALDEN, a specific algorithm for causality assessment in SJS/TEN. Incidences were estimated for both regions and drugs separately by comparing number of observed cases with number of incident drug users estimated from the database IMS® Disease Analyzer.

Results: Allopurinol-induced SJS/TEN was found in 13 patients from Ile de France and 113 patients from Germany. The incidence of allopurinol-induced SJS/TEN among 100 000 incident allopurinol users was estimated as 4.9 (95% confidence interval [CI]: 2.6–8.4) for Ile de France and 1.6 (95%CI: 1.3–2.0) for Germany.

No case of SJS/TEN exposed to febuxostat in the relevant time period was identified in the registry. As febuxostat was introduced recently, available data are too limited to allow for incidence estimation.

Conclusions: A series of SJS/TEN cases could be associated with allopurinol leading to a clearly raised incidence in both regions. Besides several advantages but also limitations of this study, the difference in incidence estimates between Ile de France and Germany is remarkable. Although there are several possible explanations, for example, genetic differences and differences in drug usage, these are not convincing enough and require further exploration.

Although no case of SJS/TEN related to febuxostat could be identified in the registry, a risk of febuxostat to cause SJS/TEN cannot be excluded at present stage, and further surveillance is needed.

591. Drugs and Ventricular Repolarization in a General Population: The Rotterdam Study

Maartje N. Niemeijer,[1] Marten E. van den Berg,[1] Oscar H. Franco,[1] Albert Hofman,[1] Jan A. Kors,[1] Bruno H. Stricker,[1] Mark Eijgelsheim,[1] Peter R. Rijnbeek.[1] *[1]Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands.*

Background: Prolonged ventricular repolarization (measured as heart-rate corrected QT (QTc) prolongation or JT interval prolongation) is a risk factor for ventricular arrhythmias and can be drug induced. Regulatory agencies recommend avoiding concomitant use of multiple QTc-prolonging drugs, but evidence is lacking to what degree ventricular repolarization is influenced by concomitant use of these drugs.

Objectives: The aims were to study the degree of QTc and JT interval prolongation associated with use of definite and possible QTc-prolonging drugs and to study whether concomitant use of multiple QTc-prolonging drugs is associated with additional QTc prolongation.

Methods: Within a population-based cohort of persons aged 45 years and older, with up to five electrocardiograms recorded per participant between 1991 and 2010, we used generalized estimating equations to study the association between QTc-prolonging drug use, concomitant use of multiple QTc-prolonging drugs, and repolarization duration. We adjusted the analyses for heart rate.

Results: The study population consisted of 13 009 participants with 26 908 electrocardiograms. The mean age at baseline was 65.4 ± 10.0 years, and 58% were women. Use of one definite QTc-prolonging drug was associated with a 15.4 milliseconds (95%CI: 13.1, 17.7) longer QTc and an 11.1 milliseconds (95%CI: 9.0, 13.1) longer JT interval. Concomitant use of two definite QTc-prolonging drugs occurred during only 15 ECGs and was associated with a 16.9 milliseconds (95%CI: −12.1, 46.0) longer QTc interval compared to nonusers. Use of at least one possible QTc-prolonging drug was associated with a 3.1 milliseconds (95%CI: 0.6, 5.7) longer QTc and 2.2 milliseconds (95%CI: 0.1, 4.4) longer JT interval.

Conclusions: In this study, use of definite QTc-prolonging drugs was associated with a substantially longer QTc and JT interval, whereas use of possible prolonging drugs was only associated with a small increase. The added prolongation in users of two definite QTc-prolonging drugs on QTc was small. Further research in larger or high-risk populations is needed to establish whether it is safe to use multiple QTc-prolonging drugs concomitantly.

592. Risk of Hospital Admission for Liver Injury in Users of NSAIDs and Non-overdose Paracetamol (EPIHAM)

Ezgi Gulmez,[1] Régis Lassalle,[1] Jérémy Jové,[1] Guillaume Caridade,[1] Adeline Grolleau,[1] Nicholas Moore.[1] [1]*Pharmacology, Université de Bordeaux, Bordeaux, France.*

Background: In the SALT study, we had found similar per-user risk of acute liver failure leading to liver transplantation (ALFT) between NSAIDs and a threefold to fourfold higher rate of ALFT in non-overdose paracetamol (NOP) users.

Objectives: The aim of this study was to identify the risks of hospital admission for acute liver injury (ALI) associated with NSAIDs and NOP.

Methods: Design: Historical case-population study in the 1/97 sample of the French population healthcare database. Setting: Cases of ALI were identified in hospital discharge summaries ICD-10-codes K71.1, 71.2, 71.6, 71.9 (acute toxic liver injury) and 72.0 (hepatic failure) from 1 January 2009 to 31 December 2013 (5 years). Exposure: For cases, NSAID or paracetamol dispensation resulting in exposure within 30 days before admission. Population exposure was measured as number of patients using the drugs over the study timeframe, as total number of DDD dispensed and average number of DDD per user.

Results: Seventy-five cases were identified. Fifteen had been exposed to NSAIDs and 27 to paracetamol (alone or combined with opiates). Event rates per million DDD ranged from 0.61 [0.17–1.56] (ketoprofen) to 1.43 [0.04–7.97] (diclofenac combinations), 0.49 [0.28–0.81] for all NSAIDs combined and 0.68 [0.44–1.00] for paracetamol. There was no association with average duration of treatment. Per patient risk ranged from 24 [8–57] (ibuprofen) to 101 [3–562] (glucosamine) per million users, 43 [24–71] for all NSAIDs combined and 62 [40–91] for NOP. There was a relation between increasing average duration of treatment and increasing risk.

Conclusions: The risk profiles of NSAIDs and NOP concerning hospital admissions for ALI were similar and indicative of a type A (pharmacological or toxicological) reaction, in contrast with the ALFT, which had a pattern suggestive of type B (genetic or allergic) reactions. The threefold higher risk with paracetamol for ALFT was not found for ALI. Event rates for ALI were not predictive of risk of ALFT. ALI and ALFT probably have different mechanisms and risks, even if one may be the prelude to the other.

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593. Heterogeneity on Case Definition and Diagnostic Method of Lipodystrophy among HIV-infected Patients on Antiretroviral Therapy

Lorena G. C. Lana,[1] Daniela R. G. Junqueira,[1,2] Edson Perini,[1] Cristiane A. Menezes de Padua,[1] Letícia Penna Braga. *[1]Farmácia Social, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; [2]Faculty of Health Sciences, University of Sydney, Sydney, Australia.*

Background: Lipodystrophy is a major adverse reaction to long-term use of antiretroviral therapy (ART). In spite of this, standardization on its definition and diagnostic method are lacking.

Objectives: This study aimed to estimate the occurrence of lipodystrophy among HIV-infected patients exposed to ART.

Methods: A systematic review of the literature was carried out through a sensitive search on five databases—MEDLINE, CINAHL, LILACS, EMBASE and International Pharmaceutical Abstracts until June 2014. Observational studies investigating the occurrence of lipodystrophy as primary or secondary outcome and comparing HIV-infected patients on different ART during at least 6 months were considered eligible. The main measure of occurrence was the frequency (incidence and prevalence) of lipodystrophy, lipoatrophy and lipohypertrophy.

Results: Twenty studies (12 cross-sectional and eight prospective) were included in the systematic review. Most studies (80%) provided detailed information on the definition of lipodystrophy, describing the anatomical sites, and four (20%) reported the outcome in vague and unspecific terms. All the studies investigated morphological alterations in the abdomen, face and members, and other anatomical sites. The diagnostic method varied among the studies ($n=4$; 20%), being the concomitant evaluation of the physician and the patient the most used ($n=9$; 45%). Considering the reported nomenclature in the primary studies, the prevalence of lipodystrophy ranged between 11.7% and 67.8%. The most prevalent phenotype was mixed lipodystrophy (39.9%). The incidence of lipodystrophy ranged between 8.1% and 52.0%. The occurrence of the outcome was mainly investigated in relation to comparative exposures between exposed and non-exposed to protease inhibitors ($n=4$; 26.7%) and between zidovudine and stavudine ($n=4$; 26.7%).

Conclusions: Studies employed very different definitions of lipodystrophy and of its diagnostic methods. It precluded the estimation of a more precise measure of occurrence of this adverse reaction and a comparative evaluation of the risk determinants.

594. Initiative to Improve Recruitment to a Streamlined Safety Study by Providing Study Information in a More Accessible Format

Robert Flynn,[1] Claudine Jennings,[1] Wendy Saywood,[1] Isla Mackenzie,[1] Evelyn Findlay,[1] Kay Walker,[1] George Nuki,[2] Ian Ford,[3] Thomas MacDonald.[1] *[1]Medicines Monitoring Unit, University of Dundee, Dundee, UK; [2]University of Edinburgh, Edinburgh, UK; [3]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK.*

Background: Randomised studies such as the Febuxostat versus Allopurinol Streamlined Trial (FAST) represent a relatively low-cost way to meet post-licencing regulatory requirements and establish causality between drug exposure and safety outcomes. Recruiting patients is challenging, with typically only one in seven patients invited to participate being randomised. Strategies are needed to improve this. We hypothesised that providing patients with study information in a user-friendly DVD format would improve recruitment.

Objectives: The aim of this study was to establish whether sending subjects a DVD explaining the background and operation of FAST would increase the proportion of patients replying to and accepting the invitation.

Methods: Patients invited to screen for FAST were randomly supplied with either the standard invitation (a letter and patient information sheet) or the standard invitation plus a DVD. These were sent to subjects invited to participate in FAST from primary care practices in Scotland from August 2013 to July 2014. The proportion of patients responding and responding positively is described, and comparisons between groups are made using a χ^2-test. The Scottish Index of Multiple Deprivation (a crude measure of socioeconomic status) was linked using the subjects' partial postcode.

Results: A total of 1050 subjects were included from 58 primary care practices. Five hundred and nine were allocated to receive the standard invitation plus DVD and 541 the standard invitation only. The groups were balanced for age, sex and social deprivation. A reply was received from 267 (52.5%) subjects who received

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the standard invitation plus DVD and 316 (58.4%) who received the standard invitation only ($\chi^2 = 3.77$; df = 1; $p = 0.0523$). A positive reply was received from 144 (28.3%) who received the standard invitation plus DVD and 181 (33.5%) subjects who received the standard invitation only ($\chi^2 = 3.27$; df = 1; $p = 0.0704$). Being male and having a lower level of deprivation were factors associated with a positive reply.

Conclusions: The addition of a DVD had no impact on the number of replies or positive replies to the invitation to participate. Further strategies are needed to boost patient participation in clinical trials.

595.Observations of Progressive Multifocal Leukoencephalopathy (PML) in Patients with Systemic Lupus Erythematosus (SLE): Systematic Literature Review

Amanda Eudy,[1,2] Cassidy Henegar,[1] Vineetkumar Kumar,[1] Dimitri Bennett,[1] Barbara Haight,[3] Eric Lewis,[3] Deanna Hill.[1] *[1]Worldwide Epidemiology, GlaxoSmithKline, Research Triangle Park, NC, USA; [2]University of North Carolina at Chapel Hill Gillings School of Global Public Health, Chapel Hill, NC, USA; [3]Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Research Triangle Park, NC, USA.*

Background: PML is a rare but serious and often fatal disease of the central nervous system. PML has been reported in immunosuppressed patients, namely HIV, but also in patients with SLE, potentially due to immunosuppressive medication exposure, underlying disease, or combination of both. The incidence of PML is 0.3–0.8/100 000 person-years (PY) in the general population and 130/100 000 PY in HIV patients.

Objectives: This study aimed to determine risk factors for PML in SLE patients and how underlying disease or treatment for SLE may be associated with PML in this population.

Methods: Studies of any design published in English (01 January 1984 to 31 October 2014) that reported PML and SLE in adult patients were searched in PubMed, Embase, and Scopus. Immunosuppression was defined as exposure to ≥1 immunosuppressant drugs of interest at PML diagnosis: belimumab, rituximab, mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, high-dose corticosteroids (>15 mg/day), and others. Minimal immunosuppression was defined as low-dose corticosteroids (≤15 mg/day) and/or hydroxychloroquine. This was an internal GlaxoSmithKline review where two independent reviewers completed article abstractions.

Results: Thirty-four publications met our inclusion criteria: four observational studies, two large case series, and 28 case reports that described 34 cases of PML in SLE patients. Reported PML incidence rates among SLE patients based on observational studies ranged from 1.0 to 2.4 cases/100 000 PY. Of the 34 case reports, 29 were female, median age of 43 years at PML diagnosis. PML was diagnosed by MRI ($n = 29$), brain biopsy ($n = 23$), and/or JC virus positive cerebral spinal fluid ($n = 16$). Three cases were exposed to no immunosuppressant drugs at PML diagnosis, four cases had minimal immunosuppression, 23 cases had immunosuppression, and four cases were indeterminate.

Conclusions: Based on limited available data summarized in our review, SLE patients may be at increased risk of PML compared to the general population, potentially due to underlying disease, treatments prescribed to manage disease, or both. There is a need for a more systematic way of capturing rare events such as PML.

596.Risk of Hypoglycemia Associated with Sulfonylurea and Insulin or Insulin Monotherapy

Jea Young Min,[1,2] Marie R. Griffin,[1,2,3] Carlos G. Grijalva,[1,3] Robert A. Greevy,[1,4] Adriana M. Hung,[1,2] Xulei Liu,[1,4] Christianne L. Roumie.[1,2] *[1]Veterans Health Administration-Tennessee Valley Healthcare System, Geriatric Research Education Clinical Center, HSR&D Center, Nashville, TN, USA; [2]Department of Medicine, Vanderbilt University, Nashville, TN, USA; [3]Department of Health Policy, Vanderbilt University, Nashville, TN, USA; [4]Department of Biostatistics, Vanderbilt University, Nashville, TN, USA.*

Background: Many patients initially treated with sulfonylureas intensify their treatments by adding insulin or switching to insulin monotherapy. However, information about the safety of these intensification regimens, especially the risk of hypoglycemia, is limited.

Objectives: The aim of this study was to compare the risk of hypoglycemia between patients who add insulin to their sulfonylurea regimen and those who switch from sulfonylurea to insulin monotherapy.

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Methods: We identified a retrospective cohort of US veterans with type 2 diabetes who initiated treatment with a sulfonylurea from 2001 to 2008. Patients who subsequently added insulin to their regimen were 1:1 propensity score (PS) matched to those who switched to insulin monotherapy based on baseline characteristics. Hypoglycemia was defined as a hospitalization or emergency room visit due to hypoglycemia or an outpatient blood glucose measurement of <60 mg/dl. Follow-up time began 6 months of post-intensification and continued until hypoglycemia event, non-persistence on regimen, loss to follow-up, death, or end of study (30 September 2011). A Cox proportional hazards model was used to compare the risk of hypoglycemia between PS-matched treatment groups.

Results: A total of 144 110 patients received incident diabetes treatment with a sulfonylurea; 48.6% of patients never intensified treatment over an average of 50 months of follow-up. A total of 74 115 intensified their regimen, with the majority (72%) adding metformin. There were 5374 patients who intensified their regimen with insulin, including 3728 who continued sulfonylurea with insulin and 1646 who switched to insulin only. After PS matching, the cohort included 1596 patients in each group. Median duration of sulfonylurea monotherapy was 16 months, with similar baseline glycated hemoglobin (HbA1c) levels in the two groups (8.3% and 8.2%, respectively). There was no significant difference in risk of hypoglycemia between PS-matched groups (hazard ratio = 0.94, 95% confidence interval: 0.76, 1.16).

Conclusions: We found no significant difference in the risk of hypoglycemia among incident sulfonylurea users adding insulin compared to those switching to insulin monotherapy.

597. Effect of Antimalaria Prophylaxis with Sulfadoxine–Pyrimethamine on Pregnancy Outcomes

Nneka U. Igboeli,[1] Chibunna J. Mbaeri,[1] Cletus N. Aguwa.[1] *[1]Clinical Pharmacy & Pharmacy Mgt, University of Nigeria, Nsukka, Enugu, Nigeria.*

Background: Malaria is associated with unfavourable pregnancy outcomes for both the mother and child, particularly in high malaria transmission areas like Nigeria. These adverse outcomes include maternal morbidity, low birth weight, preterm deliveries and perinatal mortality (stillbirth). Intermittent preventive therapy in pregnancy with sulfadoxine–pyrimethamine (IPTp-SP) is recommended for all pregnant women in malaria endemic zones in order to prevent these adverse pregnancy outcomes.

Objectives: This study aimed to evaluate the effect of IPTp-SP use on the risk of having unfavourable pregnancy outcomes.

Methods: Relevant obstetric data (e.g. IPTp-SP use) matched against pregnancy outcome data, such as delivery method, stillbirth, maternal haematocrit test results and babies' birth weights, were collected retrospectively from antenatal care (ANC) case files of women that delivered within a 1-year period (2013) at a secondary hospital in Enugu state, Nigeria. Low birth weight (LBW) was defined as baby's birth weight <2.5 kg and maternal anaemia as haemoglobin content (Hb) <11 g/dL. Associations between unfavourable pregnancy outcomes and IPTp-SP use were sought with logistic or linear regressions where applicable.

Results: A total of 500 ANC case files were used for data collection. Coverage of at least one-dose IPTp-SP was 68.4%. There were significantly reduced odds of LBW (OR: 0.26[0.09–0.75], $p = 0.012$), stillbirth (OR: 0.10 [0.06–0.18], $p < 0.0001$), caesarean section (OR: 0.36 [0.24–0.53], $p < 0.0001$) and maternal anaemia (OR: 0.33 [0.17–0.63], $p < 0.0001$) among women receiving IPTp-SP. Also, positive significant mean differences were observed for birth weight (0.199 kg [0.080–0.318], $p = 0.001$) and haemoglobin concentration (4.048 g/dL [2.53–5.57], $p < 0.0001$)

Conclusions: Adverse pregnancy outcomes were significantly reduced in women that received IPTp-SP when compared to those that did not received IPTp-SP.

598. Outcomes of Facility-level Use of Ferumoxytol versus Other Intravenous Iron Formulations in Incident Hemodialysis Patients

Medha Airy,[1] Sreedhar Mandayam,[1] Aya A. Mitani,[2,3] Tara I. Chang,[3] M. Alan Brookhart,[4] Benjamin A. Goldstein,[3,5] Wolfgang C. Winkelmayer.[1,3] *[1]Baylor College of Medicine, Houston, TX, USA; [2]Boston University School of Public Health, Boston, MA, USA; [3]Stanford University School of Medicine, Palo Alto, CA, USA; [4]University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC, USA; [5]Duke University School of Medicine, Durham, NC, USA.*

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Background: Ferumoxytol was approved in 2009 based on data from trial comparisons with oral iron and solely on biochemical anemia efficacy endpoints.

Objectives: The aim of this study was to compare the rates of hard outcomes (infection, cardiovascular [CV] risk, and death) between ferumoxytol and intravenous iron sucrose (IS) or ferric gluconate (FG) in patients with end-stage renal disease (ESRD) initiating hemodialysis (HD).

Methods: From the US Renal Data System, we identified all HD facilities that switched (almost) all patients from IS/FG to ferumoxytol (7/09–12/11). Each switching facility was matched with three facilities that continued IS/FG use. All incident ESRD patients subsequently initiating HD in these centers were studied and assigned their facility exposure. They were followed for all-cause mortality, CV hospitalization/death, or infectious hospitalization/death. Follow-up ended at kidney transplantation, switch to peritoneal dialysis, transfer to another facility, facility switch to another iron formulation, and end of database (31/12/2011). Cox proportional hazards regression was then used to estimate adjusted hazard ratios (HR [95% confidence intervals]).

Results: In 7/2009–12/2011, 278 HD centers switched to ferumoxytol; 265 units (95.3%) were matched with three units each that continued to use IS/FG. Subsequently, 14 206 patients initiated HD, 3752 (26.4%) in ferumoxytol, and 10 454 (73.6%) in IS/FG centers; their characteristics were very similar. During 6433 person-years, 1929 all-cause, 726 CV, and 191 infectious deaths occurred. Patients in ferumoxytol (versus IS/FG) facilities experienced similar all-cause (HR = 0.95 [0.85–1.07]), CV (HR = 0.99 [0.83–1.19]), and infectious mortality (HR = 0.88 [0.61–1.25]). Among 5513 Medicare (parts A + B) beneficiaries, CV events (myocardial infarction, stroke, and CV death; HR = 1.05 [0.79–1.39]) and infectious events (hospitalization/death; HR = 0.96 [0.85–1.08]) did not differ between the iron exposure groups.

Conclusions: In incident HD patients, ferumoxytol showed similar short-term to mid-term safety profiles with regard to CV, infectious, and mortality outcomes compared with the more commonly used intravenous iron formulations, IS and FG.

599. Comparative Effectiveness and Safety of SSRI Treatment with or without Concomitant Use of Statins: A Population-based Study

Ole Köhler,[1] Christiane Gasse,[2] Ole Mors,[1] Andrew Nierenberg,[3] Liselotte Petersen,[2] Søren Dinesen Østergaard.[1] *[1]Research Unit P, Aarhus University Hospital, Risskov, Denmark; [2]National Centre for Register-based Research, Aarhus University, Aarhus, Denmark; [3]Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.*

Background: Clinical trials have indicated that the combination of selective serotonin reuptake inhibitors (SSRIs) and statins may have superior antidepressant effects compared to SSRI treatment alone.

Objectives: The aim of this study was to investigate if this beneficial effect can be generalized to more heterogenic populations of SSRI users and whether the SSRI + statin combination is safe.

Methods: Nationwide cohort study focused on all incident SSRI users (i.e. no SSRI or statin use in the previous year) in Denmark between 1997 and 2012. Using Cox regression and competing risk analysis, the incidence rates of events during exposure periods of concomitant use of SSRIs and statins were compared with incidence rates during exposure periods of SSRI treatment only for any psychiatric hospitalization, psychiatric hospitalization due to depression, suicidal events (completed or attempted suicide), and all-cause mortality. Results are reported as crude and adjusted hazard rate ratios (cHR and aHR, respectively) with 95% confidence intervals (95%CI) adjusted for age, gender, education, year of SSRI initiation, previous psychiatric and somatic disorders, and previous psychiatric and somatic medication use.

Results: We identified 872 216 incident SSRI users (total follow-up: 642 058.4 person-years) of whom 113 108 (13.0%) used statins concomitantly. Compared to SSRI treatment alone, the combined use of a SSRI and a statin was associated with lower risks for psychiatric hospitalizations [number (N) = 89 906; cHR = 0.65 (0.60; 0.71); aHR = 0.75 (95%CI = 0.69; 0.82)] and for psychiatric hospitalization due to depression [N = 33 168; cHR = 0.63 (0.58; 0.68); aHR = 0.77 (95%CI = 0.70; 0.84)]. Regarding safety, compared to SSRI treatment alone, concomitant use of SSRIs and statins was associated with no increased all-cause mortality [N = 40 075; cHR = 1.00 (0.93; 1.08); aHR = 1.03 (95%CI = 0.96; 1.12)] and no increased risk for suicidal events [N = 7217; cHR = 0.79 (0.56; 1.10); aHR = 0.85 (95%CI = 0.61; 1.18)]. All results were robust across gender, age groups, and several sensitivity analyses.

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Conclusions: Concomitant use of SSRIs and statins may represent a safe adjunctive antidepressant treatment option.

600. Effectiveness of Medication in Preventing Psychiatric Hospitalization in Bipolar Disorder—A Swedish Register-based Study

Erik Joas,[1] Alina Karanti,[1] Paul Lichtenstein,[2] Mikael Landén.[1] *[1]Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, Sweden; [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.*

Background: Bipolar disorder is a severe psychiatric disorder, and long-term pharmacological treatment aimed at preventing new episodes is a cornerstone of treatment. Randomized controlled trials (RCT) have demonstrated efficacy for several drugs. Generalizability of these findings to naturalistic settings is difficult since many studies use enriched designs and exclude patients with psychiatric comorbidity.

Objectives: The aim of this study was to assess the effectiveness of lithium, three anticonvulsant drugs and two atypical antipsychotics in preventing psychiatric hospitalization among patients with bipolar disorder in a naturalistic setting. As secondary outcomes, we analyzed hospitalizations due to manic, depression and mixed episodes.

Methods: Through a linkage of Swedish national registries, we identified 35 182 people with bipolar disorder, their medication and hospitalization between 2006 and 2009. The effectiveness of lithium, valproate, lamotrigine, carbamazepine, quetiapine and olanzapine was assessed using Cox regressions in both within-individual and between-individual models.

Results: Our within-individual analyses demonstrated a protective effect of lithium (hazard ratio (HR): 0.66, 95% confidence interval (CI): 0.63–0.71), valproate (HR: 0.72, 95%CI: 0.67–0.79), lamotrigine (HR: 0.79, 95%CI: 0.73–0.84), quetiapine (HR: 0.80, 95%CI: 0.73–0.87) and olanzapine (HR: 0.76, 95%CI: 0.70–0.82) for any psychiatric hospitalization. Lithium, valproate, carbamazepine, quetiapine and olanzapine demonstrated protective effects against manic episodes. Lithium, valproate, lamotrigine, quetiapine and olanzapine showed protective effects against depression.

The between-individual analyses showed potential confounding-by-indication, for example, antipsychotics were associated with higher risk of psychiatric hospitalization.

Conclusions: Our study corroborates results from RCTs on the prophylactic effect of several medications used in maintenance treatment of bipolar disorder, which is reassuring both for patients and for clinicians. However, results for the newer antipsychotics were not as strong as previous RCTs have shown.

601. Effects of Reformulating OxyContin on Opioid Abuse in 6 National US Abuse Surveillance Systems

Paul M. Coplan,[1] Howard D. Chilcoat.[1] *[1]Risk Management & Epidemiology, Purdue Pharma L.P., Stamford, CT, USA; [2]Epidemiology, Adjunct, University of Pennsylvania School of Medicine, Philadelphia, PA, USA.*

Background: Opioids have analgesic benefits and potential risks including abuse, addiction, and overdose. Abuse-deterrent opioid formulations may manage the risks while preserving benefits for patients.

Objectives: The aim of this study was to assess the effects of the reformulation of OxyContin® (ERO) with physicochemical abuse-deterrent properties that make tablets harder to crush, dissolve, or chew on rates of ERO abuse compared to other opioids in six national surveillance systems at 3 years after reformulation.

Methods: Data from six surveillance systems were examined: (1) National Poison Data System (NPDS), (2) RADARS® Poison Center(PC) Program, (3) NAVIPPRO® ASI-MV system assessing individuals in substance abuse treatment, (4) RADARS Drug Diversion program using law enforcement officials' surveillance, (5) doctor shopping using IMS prescription data, and (6) spontaneous adverse event reports of fatalities to the manufacturer. Changes in abuse rates were compared from the year before (July 2009 to June 2010) to 3 years after (January 2011 to June 2013) reformulation of ERO. From July 2010 to December 2010 was considered a transition period. Comparator opioid groups were (a) scheduled two and three opioid tablets (excluding ERO, methadone, and patches) and (b) immediate-release oxycodone.

Results: Compared to the year prior to reformulation, there were large decreases in abuse rates of ERO in all six surveillance systems in the 3 years after ERO

reformulation: 55% decrease ($p < 0.001$) in NPDS, 55% decrease ($p < 0.001$) in RADARS PC, 48% decrease ($p < 0.001$) in NAVIPPRO system assessing individuals in substance abuse treatment, 61% decrease ($p < 0.001$) in RADARS Drug Diversion program using law enforcement officials' surveillance, and 50% decrease in doctor shopping rates for ERO nationally. Reductions for ERO were significantly greater than changes for the two comparator opioid groups. Spontaneously reported overdose fatalities reported to the manufacturer decreased 87% by the third year, while non-fatal ERO reports did not decrease post-reformulation.

Conclusions: These findings indicate that abuse of ERO decreased after its reformulation and the decrease persisted up to 3 years of post-reformulation. Additional follow-up is ongoing.

602. Metformin plus Insulin versus Metformin plus Sulfonylurea and the Associated Risk of Hypoglycemia

Christianne L. Roumie,[1,2] JeaYoung Min,[1,2] Robert A. Greevy,[1,3] Carlos Grijalva,[1,4] Adriana M. Hung,[1,2] Xulei Liu,[1,3] Marie R. Griffin.[1,4] *[1]Geriatric Research Education Clinical Center (GRECC), Veterans Health Administration-Tennessee Valley Healthcare System, Nashville, TN, USA; [2]Department of Medicine, Vanderbilt University, Nashville, TN, USA; [3]Department of Biostatistics, Vanderbilt University, Nashville, TN, USA; [4]Department of Health Policy, Vanderbilt University, Nashville, TN, USA.*

Background: Understanding the risk of hypoglycemia associated with diabetes treatment intensification regimens can inform regimen selection, but this information is lacking.

Objectives: We compared risk of hypoglycemia between metformin initiators who added insulin or sulfonylurea.

Methods: We constructed a retrospective cohort using the National Veterans Health Administration, Medicare, and the National Death Index databases. Eligible veterans included those initially treated with metformin (2001–2008) who added either insulin or sulfonylurea. Each insulin intensifier was propensity score (PS) matched by baseline characteristics to five sulfonylurea intensifiers. Patients were followed through September 2011. Risk of first and recurrent hypoglycemia was compared between therapies using PS matching and Cox proportional hazard models to adjust for baseline and time-varying demographics, medications, hemoglobin A1c, creatinine, blood pressure, body mass index, and co-morbidities. Hypoglycemia events encompassed hospitalization or emergency department visit for hypoglycemia or an outpatient blood glucose value <60 mg/dL.

Results: Among 178 341 metformin monotherapy patients, 2948 and 39 990 added insulin or sulfonylurea, respectively. PS matching yielded 2436 metformin + insulin and 12 180 metformin + sulfonylurea patients. At intensification, the median (interquartile range) time on metformin was 14 months (5, 30), and HbA1c was 8.1% (7.2, 9.9). There were 121 versus 466 first hypoglycemia events among those who added insulin versus sulfonylureas, respectively. Hypoglycemia rates were 30.9 versus 24.6 events per 1000 person-years, respectively; the adjusted HR was 1.26 (95%CI: 1.037, 1.54, $p = 0.023$) for the PS-matched analysis. When allowing for recurrent hypoglycemic events, there were 146 and 542 hypoglycemic events (27.7 and 35.9 per 1000 person years, adjusted HR of 1.31, 95%CI: 1.06, 1.63, $p = 0.02$). Results were robust to sensitivity analyses.

Conclusions: In a large cohort of patients on metformin monotherapy, for 1000 patients intensifying metformin with insulin versus sulfonylurea, there were between 6 and 8 additional clinically detectable hypoglycemia events annually.

603. Associations between Lithium and Suicide and Nonsuicide Death among Veterans Health Administration Patients

Eric G. Smith,[1,2] Karen L. Austin,[3,4] Hyungjin M. Kim,[3,4,5] Susan V. Eisen,[1,6] Amy M. Kilbourne,[3,7,8] Donald R. Miller,[1,6] Kara Zivin,[3,4,8] Claire Hannemann,[3,4] Brian Sauer,[9,10] Marcia Valenstein.[3,4,8] *[1]Center for Healthcare Organization and Implementation Research, Edith Nourse Rogers Memorial Veterans Affairs Medical Center, Bedford, MA, USA; [2]Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA; [3]Serious Mental Illness Treatment Resource and Evaluation Center, Department of Veterans Affairs, Ann Arbor, MI, USA; [4]Center for Clinical Management Research, VA Health Services Research and Development, Ann Arbor, MI, USA; [5]Center for Statistical Consultation and Research, University of Michigan, Ann Arbor, MI, USA; [6]Department of Health Policy and Management, Boston University School of Public Health, Boston, MA, USA; [7]Quality Enhancement Research*

Initiative (QUERI), Department of Veterans Affairs, Washington, DC, USA; [8]Department of Psychiatry, University of Michigan Medical School, Ann Arbor, MI, USA; [9]VA IDEAS2.0 Center, Department of Veterans Affairs, Salt Lake City, UT, USA; [10]Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA.

Background: Lithium (Li) has been previously associated with lower suicide and nonsuicide mortality.

Objectives: The aim of this study was to examine a priori hypotheses that Li would be associated with lower suicide and nonsuicide death among veterans.

Methods: New user, historical prospective cohort study of 93,000 Veterans Health Administration patients with mental health disorders initiating Li or valproate (VAL) from 1999-2008 using 1:1 high-dimensional propensity score matching. Risks of suicide and nonsuicide death over 365 days of treatment were estimated by stratified Cox regression, except for patients discontinuing treatment (non-stratified Cox regression).

Results: Li was associated with increased intent-to-treat risks of suicide death among patients with bipolar disorder (HR = 1.50 [95%CI: 1.05–2.15]) but not patients without bipolar disorder (HR = 0.77 [0.49–1.21]). Secondary analyses indicated nonsignificantly higher risks among patients with bipolar disorder after discontinuing Li (HR = 2.05 [0.88–4.79]) but not when receiving Li (HR = 1.0 [0.52–1.92]). Li was associated (among all patients combined) with nonsignificantly lower intent-to-treat risks of nonsuicide death (HR = 0.92 [0.82–1.04]) but significantly lower risks among patients receiving Li (HR = 0.62 [0.45–0.84]). Over the first 180 days (but not 365 days), significant nonsuicide mortality was observed among patients discontinuing Li (HR = 1.54 [1.01–2.37]).

Conclusions: In intent-to-treat analyses, Li was associated with higher risk of suicide among patients with bipolar disorder, apparently attributable to risks after discontinuation (which may indicate confounding or new onset risks from discontinuation). Evidence to be discussed (e.g., risks in unmatched patients and external calibration) suggested any residual confounding biased towards higher risks for Li (suicide death) and VAL (nonsuicide death). Thus, the finding least likely to be wholly or partly the result of confounding is the transient increased nonsuicide mortality risk among patients discontinuing Li by 180 days, since these findings run counter to likely confounding. The value of multiple approaches to infer the direction of residual confounding will be discussed.

604. Differential Postpartum Surveillance for Type 2 Diabetes in Women Treated with Glyburide versus Insulin for Gestational Diabetes

Suzanne N. Landi,[1] Wendy Camelo Castillo,[2] Kim Boggess,[3] Mitchell M. Conover,[1] Michele Jonsson Funk.[1] *[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Pharmaceutical Health Services Research, School of Pharmacy, University of Maryland, Baltimore, MD, USA; [3]Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Women with gestational diabetes (GDM) are at increased risk for developing type 2 diabetes (T2DM) and are therefore advised to receive glucose testing postpartum. Those requiring pharmacotherapy to treat GDM may require closer surveillance, but it is unknown whether surveillance differences exist between those treated with glyburide versus insulin in pregnancy.

Objectives: The aim of this study was to examine differences in administrative healthcare claims related to surveillance for incident T2DM between those treated with glyburide versus insulin for GDM.

Methods: We identified a cohort of women aged 15–50 years who had claims for delivery of a liveborn infant and who had received glyburide or insulin treatment for incident GDM in Truven Health Analytics' MarketScan database, 2001–2011. Those with a prior claim for T2DM were excluded. Women were followed prospectively from 6 weeks to 2 years postpartum to identify claims for surveillance for incident T2DM (outpatient office visits and glucose tests). We estimated Kaplan–Meier survival curves, hazard ratios, and 95% confidence intervals to compare the rates of service utilization between glyburide and insulin users controlling for age, region, calendar year, and recorded ICD-9 codes for obesity.

Results: In total, we identified 10 704 women for inclusion in our study ($n = 4876$ previously received insulin and $n = 5828$ previously received glyburide). The median follow-up time was 556 days after the index delivery date. A total of 3419 women (33.5%) in our

cohort received glucose testing between 6 weeks and 2 years postpartum. Glyburide users were less likely to receive a glucose test (aHR = 0.84, 95%CI: 0.79, 0.90), outpatient visit (aHR = 0.93, 95%CI: 0.89, 0.97), or either (aHR = 0.93, 95%CI: 0.89, 0.97) after 6 weeks postpartum, as compared with insulin users.

Conclusions: Women treated with glyburide during pregnancy were less likely to be screened for T2DM postpartum than women treated with insulin. Further investigation is needed to determine if differential rates of screening may account for observed differences in T2DM incidence between these treatment groups.

605.Long-term Effectiveness of Entecavir among Hepatitis B Patients in Taiwan

Yi-Chun Yeh,[1,2] Chun-Jen Liu,[3,4] Pei-Jer Chen,[3,4] Mei-Shu Lai.[1,2] *[1]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [2]Center for Comparative Effectiveness Research, Clinical Trial Center, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Internal Medicine and Hepatitis Research Center, National Taiwan Hospital, Taipei, Taiwan; [4]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan.*

Background: Nucleos(t)ide analogues (NAs) are commonly used antiviral drug for chronic hepatitis B, because these drugs are relatively easy to administer, present a low risk of adverse events, and have no contraindications. However, these agents are frequently occurring drug resistance, especially in lamivudine therapy. In 2005, entecavir was approved as first-line antiviral treatment for CHB patients and treatment for lamivudine-resistant CHB patients. Because of the higher rate of virological suppression and lower rate of drug resistance, entecavir has become as the first choice of NAs for treating CHB patients.

Objectives: The purpose of this study was to evaluate the long-term effectiveness of entecavir among patients with CHB.

Methods: A population-based cohort was assembled using the National Health Insurance claims data covering the period from 2008 to 2010. All patients included in the study were diagnosed with HBV and with prescriptions for entecavir within a clinical setting. The outcomes were defined as all-causes mortality, liver-related mortality, and hepatocellular carcinoma incidence. Multivariate hazard ratios were estimated using the Cox proportional hazard model.

Results: A total of 76 648 patients were diagnosed HBV and included in the final analysis, and entecavir therapy was administered to 8428 patients. The adjusted hazard ratios (95% confidence interval) for entecavir compared with untreated group were as follows: 0.63 (0.56–0.71) for all-causes mortality and 0.73 (0.63–0.85) for liver-related mortality, and 0.34 (0.29–0.40) for HCC incidence, respectively.

Conclusions: Entecavir use could decrease the risk of overall mortality, liver-related mortality, and HCC incidence as compared with untreated patients. These positive results support intensive efforts of antiviral treatment for HBV patients.

606. Short-term Effect on Hemoglobinemia in Epoetin Users: No Difference between Biosimilar and Originator

Ylenia Ingrasciotta,[1] Francesco Giorgianni,[1] Andrea Fontana,[2] Jenny Bolcato,[3] Roberta Pirolo,[3] Alessandro Chinellato,[3] Achille Patrizio Caputi,[1] Gianluca Trifirò.[1] *[1]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [2]Unit of Biostatistics, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy; [3]Treviso Local Health Unit, Treviso, Italy.*

Background: Since 2007, biosimilar of epoetin alpha is available on the Italian market. Very limited post-marketing data exist on the comparative effectiveness of biosimilar and originator epoetins.

Objectives: This study aimed to evaluate and compare the short-term effects of biosimilars and originators on hemoglobinemia (Hb), quantified as the pre-treatment and post-treatment difference in Hb values (delta Hb) in chronic kidney disease (CKD) or cancer outpatients in a Local Health Unit (LHU) from Northern Italy.

Methods: A retrospective cohort study was conducted during the years 2009–2013 using the Treviso LHU claims database. Incident epoetin treatments (IET) (no epoetin prescriptions within 6 months prior to treatment) with at least one Hb registration within 3 months prior and after of starting treatment date (index date) were identified. The median along with interquartile range (IQR) for biosimilar and originator epoetin consumption,

as n° of defined daily dose (DDD), during the first 3 months of treatment, was separately reported. Delta Hb within the first 3 months prior/after starting treatment, by type of epoetin, was evaluated. IET were classified as non-responders (delta Hb < 0 g/dl), responders (0 < delta Hb ≤ 2 g/dl) and highly responders (delta Hb > 2 g/dl).

Results: Overall, 893 IET (CKD: 539, 60.4%; cancer: 354, 39.6%) were identified. Baseline characteristics (including age, sex and burden comorbidities) were comparable between biosimilars and originators. No statistically significant difference in DDD consumption was found between originators (median: 34.8, IQR: 20.0–80.0) and biosimilars (median: 30.0, IQR: 16.0–50.0), respectively ($p < 0.001$). No differences were observed in proportion of responders (or highly responders) between biosimilar (82.0%) and originator (80.0%) IET.

Conclusions: No difference on the short-term effects on hemoglobinemia between users of either biosimilar or originator epoetin was observed in an outpatient setting from Northern Italy. A similar DDD consumption during the first 3 months of biosimilar/originator treatment was measured, thus suggesting that lowest cost epoetin should be prescribed in CKD/cancer patients, irrespective of epoetin type.

607. Comparative Effects of Antihypertensive Medications on Colorectal Cancer Risk

Phyo T. Htoo,[1] Til Stürmer,[1] Michele J. Funk,[1] Virginia Pate,[1] Jennifer L. Lund.[1] [1]*Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: *In vivo* and *in?vitro* evidence suggests that angiotensin II may reduce the risk of colorectal cancer (CRC). Non-experimental studies evaluating the effect of angiotensin converter enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) on CRC risk report conflicting results.

Objectives: The aim of this study was to compare the risk of CRC among initiators of ACEI/ARB versus thiazides (THZ).

Methods: We conducted a cohort study using a 20% random sample of Medicare beneficiaries initiating antihypertensive monotherapy with an ACEI, ARB, or THZ from 2007 to 2012, requiring 6 months free of any antihypertensive medication. We excluded individuals with prevalent cancer in the year prior to initiation through the second antihypertensive prescription. Follow-up began 6 months after the second prescription (cancer induction period) until the earliest date of (1) medication change (discontinuation, switch, or augmentation) + 180 days, (2) ≥2 CRC diagnosis codes, (3) end of enrollment/study, or (4) ≥2 diagnosis codes for any other cancer. We estimated adjusted hazard ratios (HRs) and 95% confidence intervals (CI) using Cox proportional hazards models and robust standard errors adjusting for measured confounders using inverse probability of treatment weighting (IPTW). Sensitivity analyses included a 1-year induction period and an intention to treat (ITT) approach.

Results: We identified 88 589 initiators (65 396 ACEI/ARB and 23 193 THZ), with median follow-up times of 0.58 and 0.53 years, respectively. The incidence rate of CRC was 239.90 and 234.24 per 100 000 person-years for ACEI/ARB and THZ, respectively. After IPTW, the risk of CRC was similar for initiators of ACEI/ARB compared with initiators of THZ (aHR = 0.99, 95%CI: 0.69, 1.41). Sensitivity analyses reveal similar estimates with a 1-year induction (aHR = 1.06, 95%CI: 0.71, 1.59) and an ITT approach (aHR = 1.03, 95%CI: 0.82, 1.28).

Conclusions: Our findings provide no support for a reduced risk of CRC after initiation of ACEI/ARB compared with a THZ. While the relatively short follow-up period reflects real-world patterns of antihypertensive treatment, our analysis cannot rule-out a possible long-term beneficial effect of ACEI/ARB use on CRC risk.

608. Effectiveness of Aldosterone Antagonist Therapy among Survivors of Acute ST-elevation Myocardial Infarction—A Nationwide Nested Case–Control Study

Hsu-Wen Chou,[1] Chao-Lun Lai,[1,2] Kin-Wei Arnold Chan,[1,3,4] Mei-Shu Lai.[1] [1]*Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan;* [2]*Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan;* [3]*Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan;* [4]*Institute of Oncology, College of Medicine, National Taiwan University, Taipei, Taiwan.*

Background: A few randomized controlled trials have showed that aldosterone antagonist reduces morbidity and mortality among patients with systolic heart

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failure. However, there is currently limited evidence concerning the effectiveness of aldosterone antagonist among survivors of myocardial infarction in clinical practice.

Objectives: The objective of this nationwide nested case–control study was to evaluate the effectiveness of spironolactone on survivors of acute ST-elevation myocardial infarction (STEMI) with clinical symptoms of heart failure (HF) in Taiwan.

Methods: We constructed a population-based inception STEMI cohort using the Taiwan National Health Insurance claims data between years 2002 and 2011. Only survivors of the first STEMI with furosemide or bumetanide treatment were included in our analysis to identify patients with clinical symptoms of HF. We excluded patients who had ever been treated with spironolactone or had been diagnosed with any renal disease within 1 year preceding the STEMI. Patients died from any cause or readmission due to HF after the index hospitalization were identified as cases, and up to 20 age-matched and sex-matched controls were selected by risk-set sampling. Conditional logistic regression was applied to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of exposure to spironolactone in all-cause mortality and readmission due to HF.

Results: Among the 5583 patients who die from any cause and 103 214 controls, 2705 (48%) and 31 697 (31%), respectively, received spironolactone (aOR, 1.66; 95%CI, 1.56–1.76). Among the 5188 patients readmission due to heart failure and 98 543 controls, 2608 (50%) and 22 617 (23%), respectively, received spironolactone (aOR, 2.82; 95%CI, 2.65–2.99). In the mean daily dosage of loop diuretics analysis, regardless of higher or lower dosage, addition of spironolactone therapy shows a positive association of mortality and readmission.

Conclusions: Addition of spironolactone to optimal medical therapy among survivors of STEMI was associated with increases in all-cause mortality and readmission due to HF.

609. Association of Treatment with Carvedilol, Bisoprolol and Metoprolol on the Risk of Mortality and Hospital Admission among Older Adults with Heart Failure

Perreault Sylvie,[1,3] De Denus Simon,[1,3,4] White Michel,[2,3,4] Guay-White Brian,[1,2,3] Bouvier Michel,[2,3] Dorais Marc,[5] Dubé Marie-Pierre.[2,3,4] *[1]Faculté de Pharmacie, University of Montreal, Montreal, QC, Canada; [2]Faculté de Médecine, University of Montréal, Montreal, QC, Canada; [3]Université de Montréal, Montreal, QC, Canada; [4]Institut de Cardiologie de Montréal, Montreal, QC, Canada; [5]StatSiences, Inc., Notre-Dame-de-l'Ile-Perrot, QC, Canada.*

Background: The long-term use of ß-blockers has been shown to improve the outcomes of patients with heart failure (HF). However, it is still disputed whether this is a class effect and, specifically, whether carvedilol or bisoprolol is superior to metoprolol tartrate.

Objectives: The purpose of this study was to compare the effectiveness of ß-blockers for patients with HF in a clinical practice.

Methods: We conducted an observational cohort study using the Quebec administrative databases to identify patients with HF who were prescribed a ß-blocker after the diagnosis of HF, for example, metoprolol tartrate, carvedilol, or bisoprolol. We used descriptive statistics to characterize the patients by the type of ß-blocker prescribed at discharge. The unadjusted mortality for users of each ß-blocker was calculated using Kaplan–Meier curves and compared using the log-rank test. To account for differences in follow-up and to control for differences among patient characteristics, a multivariate Cox proportional hazards model was used to compare the all-cause mortality, cardiovascular mortality, and HF readmission.

Results: Of the 3732 patients with HF, with a median follow-up of 3.1 years per patient, the crude annual incidence of death was 16.5% with metoprolol tartrate, 15.8% with carvedilol, and 17.5% with bisoprolol. After controlling for several different covariates, we found that carvedilol (hazard ratio [HR]: 0.95, 95% confidence interval [CI]: 0.82–1.10) and bisoprolol (HR: 1.06, 95%CI: 0.95–1.18) were not superior to metoprolol tartrate in improving survival. Similar results were observed for cardiovascular mortality. But, HF readmission rate was significantly increased from 20% to 26% with carvedilol and bisoprolol compared to metoprolol tartrate.

Conclusions: Based on observational study, we suggest no evidence of a class effect for β-blockers in older patients with HF on mortality, but the choice of ß-blocker may have impact on the rate of HF readmission.

610. Comparison of Methods to Estimate Cardiovascular Event Rates Over Time in a Diabetic Population on High-intensity Statin Therapy

Mark Danese,[2] Benjamin Taylor,[1] Villa Guillermo,[3] Lothgren Mickael.[3] *[1]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, USA; [2]Outcomes Insights, Westlake Village, CA, USA; [3]Global Health Economics, Amgen Inc. (Europe), Zug, Switzerland.*

Background: It is important to estimate the rates of cardiovascular (CV) events over time, including for economic and other simulation models and for patient-level communication. Different modeling approaches have different strengths, and there is little in the literature to compare them.

Objectives: The aim of this study was to compare four common modeling approaches to estimating a composite CV event rate over time, stratified by age and gender.

Methods: The cohort was created using the Clinical Practice Research Datalink (CPRD). Prevalent diabetic patients as of 1 January 2005 (index date) were included. Patients were excluded if they had a prior history of CV disease and if they did not receive a prescription for a high-intensity statin. Follow-up occurred until CV death, non-CV death, myocardial infarction, unstable angina, ischemic stroke, heart failure, or end of follow-up (31 December 2011 or censor). Event rates were estimated using crude rates stratified by age and gender, an exponential (constant rate) model, a flexible parametric model (Royston–Parmar), and a Cox proportional hazards model. All models included age and gender as covariates.

Results: There were 7809 patients in the cohort with an average follow-up of 7 years. All four methods provided consistent results across most of the follow-up time. The stratified crude rates and the exponential model rates were very similar, as were the flexible parametric model and Cox proportional hazards model results. Because of their time-varying nature, the flexible parametric models and the Cox models had more variability in the rate estimates. The Cox model was the most variable.

Conclusions: All four methods can generate a consistent set of event rates that are useful for a variety of purposes, particularly when rates are estimated after the rates have stabilized. The choice should depend on the need for time-varying rates. Caution should be exercised in using rates from flexible parametric models or Cox models in periods where there are few events or few subjects. Cox models are less optimal because the underlying hazard rate is not estimated as a continuous function and is therefore the least smooth.

611. Impact of Fibrates on the Cardiovascular Events in Patients with Acute Coronary Syndrome Underwent Percutaneous Transluminal Coronary Angioplasty: A Population-based Cohort Study in Taiwan

Jui Wang,[1] Zhen-Fang Lin.[2] *[1]Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan; [2]School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan.*

Background: Fibrates decrease both low-density lipoprotein cholesterol and triglyceride and increase high-density lipoprotein; however, little is known about its effectiveness on cardiovascular events in acute coronary syndrome (ACS) patients.

Objectives: The aim of this study was to use large database to assess the effectiveness of fibrates on cardiovascular events among ACS patients from the population-based cohort in Taiwan.

Methods: This nationwide population-based cohort study used administrative claims data source from the Taiwan National Health Insurance Database. A total of 250 794 ACS patients who have been discharged after their first ACS events between 2006 and 2010 were enrolled. Four groups were identified: (1) non-statin/fibrate user ($n = 85\,919$), (2) fibrate user ($n = 8574$), (3) statin user ($n = 98\,835$), and (4) fibrate plus statin user ($n = 18\,782$). Cox proportional hazards regressions were performed to estimate the risk of rehospitalization for ACS during the follow-up period.

Results: During the 6-year follow-up, hazard ratio (HR) for rehospitalization for ACS is as followed in fibrate user (HR: 1.09; 95%CI, 1.04–1.16), statin user (HR: 0.95; 95%CI, 0.92–0.98), and fibrate plus statin user (HR: 0.68; 95%CI, 0.65–0.71) compared to non-statin/fibrate user.

Conclusions: Using combination therapy of fibrate and statin had lower risk of ACS rehospitalization.

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However, the adverse effect of fibrate combined with statin should be carefully monitored.

612. Comparative Effectiveness of Carotid Artery Stenting (CAS) and Carotid Endarterectomy (CEA) among Medicare Beneficiaries Treated in Routine Clinical Practice

Jessica J. Jalbert,[1,2] Louis L. Nguyen,[3] Marie D. Gerhard-Herman,[4] Hiraku Kumamaru,[1] Lauren A. Williams,[1] Chih-Ying Chen,[1] Jun Liu,[1] Andrew T. Rothman,[1] Michael R. Jaff,[5] John D. Seeger,[1] Herbert D. Aronow,[6] Joseph A. Johnston,[7] Thomas G. Brott,[8] Christopher J. White,[9] Soko Setoguchi.[10] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA; [2]LA-SER Analytica, New York City, NY, USA; [3]Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Boston, MA, USA; [4]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [5]Division of Cardiovascular Medicine, Massachusetts General Hospital, Boston, MA, USA; [6]Cardiac Catheterization Laboratory, St. Joseph Mercy Hospital, Ypsilanti, MI, USA; [7]Eli Lilly and Company, Indianapolis, IN, USA; [8]Department of Neurology, Mayo Clinic, Jacksonville, FL, USA; [9]Ochsner Clinic Foundation, New Orleans, LA, USA; [10]Duke Clinical Research Institute, Durham, NC, USA.*

Background: Randomized trials demonstrated CAS efficacy relative to CEA, but their effectiveness among older adults treated in routine clinical practice remains unknown.

Objectives: The purpose of this study was to compare the effectiveness of CAS relative to CEA among Medicare beneficiaries.

Methods: We linked Medicare data (2000–2009) to the Society for Vascular Surgery's Vascular Registry (SVS-VR; 2005–2008) and the NCDR® Carotid Artery Revascularization and Endarterectomy Registry (CARE; 2006–2008/2009). Medicare patients aged ≥66 years were followed from CAS/CEA date until death, stroke/transient ischemic attack (TIA), 30-day myocardial infarction, and a composite endpoint of these outcomes. High-dimensional propensity scores (hd-PS) were derived using registry and claims data. The following physician and hospital variables were included in the Cox regression outcome model: past-year CAS/CEA volume for physicians (low, medium, and high) and hospitals (high versus low), hospital ownership, teaching affiliation, and hospital size. Hazard ratios (HR) were derived by registry and then combined, while allowing for different baseline hazards. Sensitivity analyses on the PS included the following: (1) matching; (2) trimming; and (3) including PS in the outcome model.

Results: Among 5254 SVS-VR (1999 CAS; 3255 CEA) and 4055 CARE (2824 CAS; 1231 CEA) patients, CAS patients were more likely to be at high-surgical risk (SVS-VR: 96.7% vs 44.5%; CARE: 71.3% vs 44.7%) and had a higher comorbidity burden. Crude outcome risks for death and stroke/TIA were higher for CAS. Mortality risks remained higher for CAS compared to CEA after adjusting for patient-level factors (HR = 1.24; 95%CI: 1.06–1.46). After further adjustment for physician and hospital-level factors, differences between CAS and CEA were attenuated or no longer present (HR for mortality = 1.13; 95%CI: 0.94–1.37). Performance was comparable across subgroups defined by sex, degree of carotid stenosis, and surgical risk. Results were consistent across registries and robust to different PS adjustment methods.

Conclusions: When comparing CAS to CEA, accounting for patient, physician, and hospital factors should be considered.

613. Unintended Pregnancies in Users of Different Combined Oral Contraceptives—Final Results from the INAS-SCORE Study

Kristina Bardenheuer,[1] Juergen Dinger,[1] Christian Franke,[1] Christine Hagemann,[1] Sabine Möhner.[1] *[1]ZEG—Berlin Center for Epidemiology and Health Research, Berlin, Germany.*

Background: Oral contraceptives are the most popular method of birth control and widely used.

Objectives: The effectiveness is compared between different combined oral contraceptives in the USA and Europe.

Methods: The 'International Active Surveillance Study—Safety of Contraceptives: Role of Estrogens' (INAS-SCORE) is being conducted as a Post-authorisation Safety Study (PASS) requested by the Medicines Evaluation Board (MEB). It is a large, prospective, controlled, non-interventional and long-term cohort study with active surveillance of the study participants. It is

conducted in the USA as well as in Austria, France, Germany, Italy, UK, Poland and Sweden.

Women are enrolled by their prescribing physician. Two cohorts are being described: Qlaira (Natazia in the USA) and other COCs. During the follow-up phase, women are contacted every 6–12 months for a maximum of 6 years and asked for information about unintended pregnancy as a secondary outcome. Self-reported pregnancies are being validated by healthcare professionals.

Results: The analysis is based on 98 234 women-years (WY) of observation and 72 160 WY of OC exposure. Overall, 608 unintended pregnancies were reported, of which 33 occurred under Qlaira use (Pearl Index: 0.2; 95%CI: 0.2–0.4) and 545 under other COC use (Pearl Index: 1.0; 95%CI: 0.9–1.1). Differences were seen between Europe and the USA, with only a limited number of pregnancies under Qlaira use in the USA. Crude, age adjusted and fully adjusted HR of Qlaira versus other COCs are as follows: for the USA: 1.5 (95%CI: 0.8–3.1), 1.7 (95%CI: 0.8–3.4) and 1.8 (95%CI: 0.9–3.5) and for Europe: 0.5 (95%CI: 0.3–0.7), 0.6 (95%CI: 0.4–0.9) and 0.7 (95%CI: 0.5–1.1). Final results will be shown at ISPE.

Conclusions: OCs have a high contraceptive effectiveness. Although the European Qlaira cohort is older, age does not seem to have the strongest effect on unintended pregnancies.

614. Similarities Regarding Diagnostic Workup Utilization in Two Data Systems

Xiaojuan Li,[1] Yong Chen,[2] Julie Chandler,[2] Cynthia J. Girman,[1,3] Til Stürmer.[1] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, USA; [2]Epidemiology, Merck & Co., Inc., Whitehouse Station, NJ, USA; [3]CERobs Consulting, LLC, Chapel Hill, NC, USA.*

Background: Differential utilization of diagnostic workup may lead to differential detection of preclinical outcomes and may have contributed to the conflicting results from studies evaluating esophageal cancer risk in oral bisphosphonate (OB) users. The workup utilization may differ by study populations using different data systems.

Objectives: The aim of this study was to examine diagnostic workup utilization including endoscopy and chest X-ray around initiation of OB and raloxifene (RA) using two data systems and its potential impact on estimating esophageal cancer risk.

Methods: OB or RA initiators, age ≥66, with no previous cancer or Barrett's esophagus diagnosis, were identified in Medicare (2007–2012) and Humana (2007–2013). Initiators who filled ≥2 prescriptions were followed for incident esophageal cancer. In each data system, we estimated standardized mortality ratio weighted risk difference (RD) of workup in the 180 days of pre-initiation and post-initiation comparing OB to RA. We compared hazards of workup in the 180 days of post-initiation using Cox regression.

Results: Initiators in Medicare (220 807 OB and 13 082 RA) compared to Humana (171 220 OB and 17 759 RA) were older (Median, OB versus RA: 76 vs 74; 74 vs 72), more likely had comorbidities including gastroesophageal reflux disorder, and used proton pump inhibitors. In Medicare, compared to RA users, OB users were less likely to have endoscopy, especially after initiation [%, pre: 3.2 vs 4.4; RD:−0.2 (−0.3, −0.1); post: 3.8 vs 5.0; RD: −1.0 (−1.1, −0.9)] but more likely to have X-ray pre-initiation and post-initiation. In Humana, the trends of differential workup utilization were similar, but magnitudes were smaller. The adjusted hazard ratios in the 6 months of post-initiation in two data systems were similar for both X-ray [1.0 (1.0–1.1) vs 1.0 (0.9–1.1)] and endoscopy [0.8 (0.7–0.9) vs 1.0 (0.9–1.1)]. Numbers of incident esophageal cancer were too small to perform comparison.

Conclusions: We found evidence for no meaningful differential diagnostic workup between OB and RA initiators. Differences in differential workup by data systems were small and may be explained by age. Our results suggest that it is appropriate to study the risk of esophageal cancer in OB and RA when longer follow-up data are available.

615. Impact of Urate Level on Cardiovascular Risk in Allopurinol-treated Patients. A Nested Case–Control Study

Kasper Søltoft Larsen,[1,3] Anton Pottegård,[1] Hanne M. Lindegaard,[3] Jesper Hallas.[1,2] *[1]Department of Public Health—Clinical Pharmacology, University of Southern Denmark, Odense, Denmark; [2]Department of Clinical Chemistry & Pharmacology, Odense University Hospital, Odense, Denmark; [3]Department of Rheumatology, Odense University Hospital, Odense, Denmark.*

Background: Gout gives rise to increased risk of adverse cardiovascular outcomes. Gout attacks can be effectively prevented with urate-lowering drugs such as allopurinol, and allopurinol potentially reduces cardiovascular risk. What target level of urate is required to reduce cardiovascular risk is not known.

Objectives: The aim of this study was to investigate the effect of achieving target plasma urate with allopurinol on cardiovascular outcomes in a case–control study nested within long-term users of allopurinol.

Methods: We identified long-term users of allopurinol in Funen County, Denmark. Among these, we identified all cases of cardiovascular events (antiplatelet trialist's collaboration composite endpoint) and sampled four controls to each case from the same population using risk-set sampling. The cases and controls were compared with respect to whether they reached a urate target below 0.36 mmol/l on allopurinol. The derived odds ratios were controlled for potential confounders available from data on prescriptions, laboratory values and inpatient and outpatient contacts.

Results: No association between treatment-to-target urate level and cardiovascular events was found (adjusted odds ratio of 1.01, 95% confidence interval 0.79–1.28). No significant effect was seen in any subgroup defined by age, gender, renal function, allopurinol dose or the achieved urate level. Overall, the doses of allopurinol used in this study were low (mean ~140 mg/day).

Conclusions: We were unable to demonstrate a link between achieved urate level in patients treated with allopurinol and risk of cardiovascular events. However, the results are limited by the low doses of allopurinol used. Possible explanations include that higher allopurinol doses are required to achieve cardiovascular risk reduction or that the cardiovascular effect of allopurinol is not mediated through low urate levels. It remains to be seen whether allopurinol has a dose–response relationship with cardiovascular events at higher doses.

616. Efficacy of Osteoporosis Pharmacotherapies in Preventing Fractures among Chronic Oral Glucocorticoids Users: A Network Meta-analysis

M. Amine Amiche,[1] Jordan M. Albaum,[1] Mina Tadrous,[1] Petros Pechlivanoglou,[1] Jonathan D. Adachi,[2] Linda E. Lévesque,[3] Suzanne M. Cadarette.[1]

[1]Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Department of Medicine, McMaster University, Hamilton, ON, Canada; [3]Department of Public Health Sciences, Queens University, Kingston, ON, Canada.

Background: Several osteoporosis drugs are approved for the prevention and treatment of glucocorticoid(GC)-induced osteoporosis. However, the evidence base for the efficacy of treatments among oral GC users is limited.

Objectives: This study aimed to examine the comparative efficacy of osteoporosis treatments among chronic oral GC users.

Methods: We updated a systematic review through to September 2013 to identify all double-blinded randomized controlled trials (RCTs) that examined osteoporosis treatments among chronic GC users. We used a network meta-analysis with informative priors to derive comparative risk ratios (RRs) and 95% credible intervals (95% CrI) for vertebral and non-vertebral fracture and mean differences in lumbar spine (LS) and femoral neck (FN) bone mineral density (BMD). Treatment ranking was estimated using the surface under the cumulative ranking curve (SUCRA) statistic. A meta-regression was completed to assess a subgroup effect between patients with prior GC exposures and GC initiators.

Results: We identified 27 eligible RCTs examining nine active comparators. Etidronate (RR: 0.35, 95% CrI = 0.15–0.86), risedronate (RR = 0.29, 95%CrI = 0.13–0.58), and teriparatide (RR = 0.04, 95%CrI = 0.001–0.38) showed better efficacy than placebo in preventing vertebral fractures; yet, no treatment effects were statistically significant in reducing non-vertebral fractures. Alendronate, risedronate, and etidronate increased LS BMD, while alendronate and raloxifene increased FN BMD. In preventing vertebral fractures, teriparatide was the most efficacious agent (SUCRA: 79%), followed by both risedronate (78%) and zoledronic acid (78%). For non-vertebral fractures, teriparatide also had the highest SUCRA (87%), followed by risedronate (77%). No subgroup effect was identified with regard to prior GC exposure.

Conclusions: Despite weak trial evidence available for fracture prevention among GC users, we identified several drugs that are likely to prevent osteoporotic fracture. Teriparatide and risedronate were associated with decreased fracture risk and were highly ranked

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in reducing fracture. More trial evidence is required to reduce uncertainty in future studies.

617. Selective Serotonin Reuptake Inhibitors (SSRIs) and Colorectal Cancer (CRC)

Monica E. D'Arcy,[1] Til Sturmer,[1] Michele Jonsson-Funk,[1] John Baron,[2] Robert S. Sandler,[1] Virginia Pate,[1] Anne Marie Meyer,[1] Melissa A. Troester,[1] Jennifer L. Lund.[1] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, USA; [2]Medicine, University of North Carolina, Chapel Hill, NC, USA.*

Background: Epidemiological and laboratory evidence suggests that some antidepressants, specifically SSRIs, may reduce the risk for CRC.

Objectives: The aim of this study was to compare the incidence of CRC across cohorts of initiators of specific SSRIs: citalopram (CIT), escitalopram (ESC), sertraline (SER), paroxetine (PRX), and fluoxetine (FLX).

Methods: Using a 20% random sample of Medicare fee for service claims (2007–2012), we identified individuals aged 65+ years who initiated a single SSRI. All initiators were required to have (1) 12+ months of continuous Medicare A/B enrollment to evaluate baseline covariates, (2) 180 days of part D and no claims for an SSRI prior to initiation, and (3) 2+ claims of the same SSRI to increase probability of drug use. We excluded individuals with any CRC-associated claims in the 12 months prior to drug initiation. Follow-up began 360 days after the date of the second prescription (empirical induction) and continued until 360 days after drug discontinuation or augmentation (latency period). CIT was the referent group for all analyses. We used logistic regression to calculate drug-specific propensity scores that included several potential confounders. We weighted the non-referent groups to CIT initiators using standardized mortality ratio weighting. Incident CRC was defined as 2+ diagnosis codes (ICD-9: 153.X or 154.X excluding 154.2–154.4) within 60 days. We estimated hazard ratios (HR) and 95% confidence intervals using weighted Cox proportional hazards models.

Results: We enrolled 394 134 persons (range: PRX = 30 103; CIT = 178 610) with a second prescription. Median duration of drug use was 185 days, IQR = (90 426) (similar for all drugs), with 117 223 individuals remaining on treatment for >365 days. Average age of initiators was 78 years, 5% were Black, and 74% were women. There were 651 events in 161 859 person-years. The incidence rate was 295, 374, 385, 405, and 443 per 100 000 person-years for FLX, PRX, SER, CIT, and ESC, respectively. Compared with CIT, weighted HR varied between 0.65 (0.27, 1.53) for FLX and 1.11 (0.80, 1.53) for ESC.

Conclusions: SSRIs may differentially affect CRC risk, although we need to extend follow-up time and rule out differential diagnostic procedures before making any conclusions.

618. Antidepressants (AD) and Colorectal Cancer (CRC)

Monica E. D'Arcy,[1] Til Sturmer,[1] Michele Jonsson Funk,[1] Robert S. Sandler,[1] John A. Baron,[2] Pate Virginia,[1] Anne Marie Meyer,[1] Melissa A. Troester,[1] Jennifer L. Lund.[1] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, USA; [2]Medicine, University of North Carolina, Chapel Hill, NC, USA.*

Background: There is evidence that some AD classes may reduce the risk for CRC, although no studies have evaluated the association between serotonin and norepinephrine reuptake inhibitors (SNRIs) and CRC.

Objectives: The aim of this study was to compare the incidence of CRC across new users of TCAs, SSRIs, SNRIs, and non-users.

Methods: Using a 20% random sample of Medicare fee for service claims (2007–2012), we identified individuals aged 65+ years who initiated an SSRI, TCA, or SNRI. Non-users were initiators of anti-hypertensives (AHT), excluding beta-blockers. All initiators had (1) 365 days of continuous Medicare A/B enrollment to evaluate baseline covariates, (2) 180+ days of part D coverage and no claims for an SSRI, SNRI, TCA, or AHT class prior to initiation, and (3) 2+ claims to increase probability of drug use. We excluded individuals with recent CRC claims. Follow-up began 360 days after the date of the second prescription (induction) and continued 360 days after drug discontinuation or augmentation (latency period). AHT was the referent group for all analyses. Incident CRC was defined as 2+ diagnosis codes (ICD-9: 153.X or 154.X excluding 154.2–154.4) within 60 days. We used logistic regression to estimate drug-specific propensity scores. We estimated hazard ratios (HR) and 95% confidence intervals using Cox proportional hazards models after weighting each group to the covariate distribution of the AHT cohort.

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Results: We enrolled 425 130 persons (SSRI = 84 313; SNRI = 12 593; TCA = 12 155; AHT = 316 069) with a second prescription. Median duration of drug use was 296 days (IQR = 140 662), with 184 955 individuals remaining on treatment for >360 days. Average age was 75 years, only 8% were Black, and 63% were women. Demographics and length of use varied by drug class. There were 1104 events in 289 248 person-years, with a crude incidence rate of 220 for TCA, 374 for SNRI, 377 for SSRI, and 386 per 100 000 person-years for AHT. Compared with AHT, the weighted HRs were 0.6 (0.01, 35) for TCA, 0.9 (0.7, 1.2) for SSRI, and 1.1 (0.1, 10) for SNRI.

Conclusions: Although this preliminary evidence suggests that some classes of AD may affect CRC incidence after 365 days of use, short length of drug use —and consequently few outcomes—limits firm conclusions despite >400K users and 6 years of data.

619. Use of Different Formulations Rivastigmine and Risk of Cardiovascular Adverse Events

Edward Chia-Cheng Lai,[1,2] Monera B. Wong,[3] Isao Iwata,[4] Yinghong Zhang,[1] Cheng-Yang Hsieh,[2] Yea-Huei Kao Yang,[2] Soko Setoguchi.[1] *[1]Duke Clinical Research Institute, Durham, NC, USA; [2]Institute of Clinical Pharmacy and Pharmaceutical Sciences, Tainan, Taiwan; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Division of Geriatric Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: The use of rivastigmine, a cholinergic agent for dementia treatment, was shown to increase the risk of cardiovascular (CV) adverse events including bradycardia, atrioventricular (AV) block, and syncope. A patch form of rivastigmine provides steady plasma concentration and may lead to lower incidence of cardiovascular effects than oral forms.

Objectives: This study aimed to evaluate the interaction between patch and oral form of rivastigmine on the above CV events.

Methods: We conducted a retrospective study and selected patients newly initiated rivastigmine or memantine from 5% Medicare databases. The outcomes included hospitalizations for AV block/syncope, or cardiovascular death. We used Cox proportional hazard model to evaluate the risk of the cardiovascular events comparing rivastigmine (or oral/patch separately) versus memantine, a NMDA receptor inhibitor with minimal cholinergic effects using high-dimensional propensity score adjustment.

Results: Among 4220 rivastigmine (1157 oral and 3063 patch) and 7739 memantine users, mean age was 81.6 (±7.3) and 82.0 (±7.4), and 74% and 73% of them were women, respectively. During the mean follow-up of 247 days, 75 (incidence rate, 33.8 per 1000 person year) and 141 (26.5) had hospitalizations, and 10 (1.9) and 7 (3.1) had cardiovascular death in rivastigmine and memantine users, respectively. Compared with memantine, the risk of AV block/syncope (hazard ratio, 1.24; 95%CI, 0.93–1.65) and cardiovascular death (1.58; 0.60–4.17) was higher in rivastigmine users regardless of formulations, although not statistically significant. When stratifying by formulations, the hazard ratios of the risk of AV block/syncope were 1.62 (1.11–2.36) in oral form and 1.03 (0.72–1.47) in patch form of rivastigmine; the risk estimates of cardiovascular death were 1.82 (0.50–6.68) in oral and 1.43 (0.45–4.61) in patch form, when compared with memantine.

Conclusions: Rivastigmine may be associated with higher risk of CV adverse events compared to memantine. Formulations of rivastigmine were associated with differential risks, especially for AV block/syncope. Patch from rivastigmine or memantine may be a better choice for high-risk patients such as those with existing AV block.

620. Comparison of Short-term versus Long-term Outcomes of West Syndrome Treatment

Marina E. Farnosova,[1,3] Tatiana F. Zharikova,[3] Rimma G. Gamirova.[1,2,3] *[1]Department of Basic and Clinical Pharmacology, Kazan Federal University, Kazan, Republic of Tatarstan, Russia; [2]Department of Pediatric Neurology, Kazan State Medical Academy, Kazan, Republic of Tatarstan, Russia; [3]Municipal Kazan Children's Hospital N 8, Kazan, Republic of Tatarstan, Russia.*

Background: To date, few well-designed randomized controlled trials have considered the treatment of West syndrome. Conclusions were limited by the overall poor methodology of the studies. Hence, it is not clear which therapy of this severe epilepsy syndrome is optimal. Hormonal treatment resolves spasms in more infants than other antiepileptics, but this may not translate into better long-term outcomes.

Objectives: The aim of this study was to compare the results of treatment of patients with West syndrome after 2 months versus 3 years of follow-up.

Methods: We conducted a retrospective observational study of 138 patients (84 boys and 54 girls) with West syndrome. We calculated risk ratio (RR with Review Manager 5.2) of favorable outcomes in the therapy using tetracosactide versus non-hormonal antiepileptic therapy after 2 months from the start of treatment. Further, we compared the clinical outcomes of hormonal versus non-hormonal therapy after the 3-year follow-up. Favorable outcome: clinical remission (the number of patients without seizures).

Results: We separated all children with West syndrome into two groups. First group included 87 children (63%) who received in treatment tetracosactide. Different antiepileptic drugs as a monotherapy and combination therapy (valproic acid, topiramate, clonazepam, vigabatrin, ethosuximide, levetiracetam, and barbiturates) were used in the second group (51 children, 37%), but they did not receive tetracosactide. Children in both groups were comparable in terms of age, sex, and disease severity. Initial response to the therapy (after 2 months of follow-up) was better in children, who received tetracosactide: 66 of the 87 patients (76%) achieved the clinical remission (lack of seizures); only half of the patients (28/51, 55%) had the favorable outcome in the second group. RR was 1.38; 95%CI [1.05–1.82], $p = 0.02$. But long-term favorable outcomes were similar in two groups (62/87 (71%) for first group and 35/51 (69%) for second group). RR was 1.04; 95%CI [0.83–1.31], $p = 0.75$.

Conclusions: We did not find benefits in the control of seizures for West syndrome patients in treatment with tetracosactide versus non-hormonal antiepileptic treatment after the 3-year follow-up.

621. Stimulant Treatment and Risk of Traffic Accidents Requiring Acute Care in Adults with Attention Deficit Hyperactivity Disorder

Daina B. Esposito,[1] Gaurav Deshpande,[1] Crystal N. Holick,[1] Stephan Lanes.[1] *[1]Safety and Epidemiology, HealthCore, Andover, MA, USA.*

Background: Attention deficit hyperactivity disorder (ADHD) increases risk of traffic accidents, while it has been suggested that stimulant treatment may reduce this risk, particularly for young adults.

Objectives: The aim of this study was to measure the effect of stimulant medication in ADHD patients on risk of traffic accidents requiring acute care.

Methods: We used the HealthCore Integrated Research DatabaseSM to conduct a case–control study of new stimulant users with ADHD, 18–55 years of age. Cases were patients with a traffic accident requiring hospitalization or ED visit. For each case, we selected five controls who were under observation when the accident occurred, matched on age, gender, and region. Pharmacy dispensings were used to classify patients on the event date as current, recent, or past stimulant users. We used conditional logistic regression to assess the relation between stimulant exposure and outcomes, conditional on covariates controlled.

Results: Stimulant use was not associated with traffic accidents overall (OR = 0.95, 95%CI: 0.71–1.27); however, there was a suggestion of a lower risk for patients aged 18–24 years (OR: 0.85, 95%CI: 0.58–1.24) but not for older adults (OR = 1.33, 95%CI: 0.68–2.61 for patients aged 24–35 years and OR = 1.19, 95%CI: 0.63-2.26 for patients aged 35–55 years). For long-acting agents, heterogeneity by age was more pronounced: for young adults aged 18–24 years, we observed OR = 0.69 (95%CI: 0.45, 1.07), and we observed higher estimates for ages 25–34 (OR = 1.86; 95%CI: 0.78, 4.45) and for ages 35–55 (OR = 1.52; 95%CI: 0.73, 3.17).

Conclusions: We observed no overall association between stimulant treatment and risk of traffic accidents requiring acute care, but imprecise associations of a lower risk of traffic accidents for young adults receiving stimulant treatment, and a higher risk of traffic accidents for older adults. Further research on ADHD treatments should consider possible heterogeneity of stimulant effects by age.

622. Comparative Risk of Glaucoma in Patients with Epilepsy Receiving Antiepileptic Drugs

Wan-Ju Annabelle Lee,[1] Chia-Cheng Edward Lai,[1] Yea-Huei Kao Yang.[1,2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng-Kung University, Tainan City, Taiwan; [2]Health Outcome Research Center, National Cheng-Kung University, Tainan City, Taiwan.*

Background: Antiepileptic drug (AED) is a mainstay in epilepsy treatment; however, it has been reported to

associate with glaucoma possibly because of the anticholinergic characteristic of AED. No study has evaluated the comparative risk of glaucoma among AEDs.

Objectives: The aim of this study was to evaluate the comparative risk of glaucoma in patients with epilepsy newly initiated AEDs, including phenytoin, oxcarbazepine, gabapentin, lamotrigine, topiramate, valproic acid and carbamazepine.

Methods: We conducted a population-based retrospective cohort study by analyzing the Taiwan National Health Insurance Research Database. We included patients aged 18 years or older who newly initiated AEDs therapy in 2005–2010. The outcome of interest was glaucoma defined by ICD-9 code 365. We used inverse probability of treatment weighting with high-dimensional propensity score to balance the characteristics of patients among groups. We used Cox proportional hazard models to compare the risk of glaucoma among AEDs.

Results: We included a total of 12 917 patients initiating AEDs, and 60.6% of them were male. Among these patients, 7954, 1279, 2530, 702, 448, 208 and 156 were phenytoin, oxcarbazepine, gabapentin, lamotrigine, topiramate, valproic acid and carbamazepine users, respectively. The incidence rate of glaucoma was highest in gabapentin (37.3 per 1000 person years) following by topiramate (37.1 per 1000 person years) and carbamazepine (20.3 per 1000 person years) users. No glaucoma was found among lamotrigine users. We found that the risk of glaucoma was higher in gabapentin (adjusted HR, 3.02; 95%CI, 1.48–6.17), topiramate, (2.76, 0.85–8.93) and carbamazepine (1.91, 1.18–3.10), when compared with phenytoin users. The risk of valproic acid and oxcarbazepine was similar with phenytoin users.

Conclusions: The risk of glaucoma was higher in the subjects receiving gabapentin, topiramate and carbamazepine compared with phenytoin. Patients receiving AEDs were suggested to be regularly monitored by ophthalmologists.

623. Prescription Opioid Use and Mortality Risk in Hemodialysis Patients

Maurice A. Brookhart,[1] Diane Reams,[1] Anne Butler,[1] Magdalene Assimon,[1,2] Jennifer Flythe,[1] Abhijit Kshirsagar.[1] *[1]Department of Epidemiology, UNC Chapel Hill, Chapel Hill, NC, USA; [2]UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC, USA.*

Background: Opioids are in widespread use among US hemodialysis (HD) patients, but little is known about their safety in this population.

Objectives: We sought to assess the comparative short-term risk of mortality among HD patients initiating a prescription opioid versus a non-steroidal anti-inflammatory drug (NSAID).

Methods: We conducted a retrospective cohort study of HD patients using detailed clinical data from a large dialysis organization merged with data from the US Renal Data System, 2004–2010. We identified patients with Medicare part D eligibility initiating a new prescription for either an opioid analgesic or NSAID with at least 30 days of supply. We excluded patients with cancer, any use of hospice services, or use of multiple opioids. We assessed treatment effects on mortality using inverse probability of treatment weighted Kaplan–Meier methods that adjusted for a large number of comorbid conditions, laboratory, and clinical variables. Survival curves were used to estimate 180-day mortality risk differences (RD) and 95% confidence intervals (CI) between opioid and NSAID groups.

Results: We identified 5113 patients who met study entry requirements, of which 3439 (67.3%) received an opioid. Relative to new NSAID users, new opioid users had similar baseline laboratory values but a slightly higher prevalence of comorbid conditions, including recent infections, cardiovascular (CV) disease, and chronic obstructive pulmonary disease (COPD). We observed an increased risk of 180-day mortality among patients starting opioids (RD: 2%, 95%CI: 0.2, 3.9%). In subgroup analyses, the mortality risk was particularly elevated among patients with a history of CV events (RD: 9.7%, 95%CI: 3.8, 14.2) and COPD (RD: 8.2%, 95%CI: 0.1, 13.6).

Conclusions: We find evidence suggesting that opioid use increases short-term mortality risk in HD patients, particularly those with CV or pulmonary disease.

624. Protective Effects of Statins in Staphylococcus aureus Bacteremia

Eunsun Noh,[1,2] Aisling R. Caffrey,[1,2] Kerry L. LaPlante.[1,2] *[1]Infectious Diseases Research Program, Veterans Affairs Medical Center, Providence, RI, USA; [2]College of Pharmacy, University of Rhode Island, Kingston, RI, USA.*

Background: Recent studies have reported anti inflammatory and immunomodulatory effects of statins. Several observational studies investigated a decreased risk of mortality among statin users with bloodstream infections; however, the protective effects of statins remain unclear.

Objectives: The aim of this study was to quantify the effects of statin use on clinical outcomes in patients with *S. aureus* bacteremia.

Methods: This national retrospective cohort study included patients admitted to Veterans Affairs hospitals with positive *S. aureus* bloodstream infections between 2002 and 2013. Pharmacy data were assessed from inpatient barcode medication administration records and outpatient dispensings. Patients receiving appropriate antibiotics within 48 hours of culture collection were selected for inclusion. We excluded patients who died or were discharged within 2 days of culture. We defined incident statin users as those initiating a statin in the 30 days prior to culture and continuing statin use during the admission. Non-users included patients without statin administration/dispensing in the year prior to culture through discharge. Propensity score-matched and quintile-adjusted Cox proportional hazards regression models quantified the effect of statins on clinical outcomes.

Results: We identified 836 statin users and 14 973 non-users. Balance in baseline characteristics between statin users and non-users was achieved within quintiles and between propensity-matched pairs (671 pairs). We observed significantly decreased length of hospital stay in patients taking statins compared to non-users (propensity-matched hazard ratio [HR]: 1.29, 95% confidence interval [CI]: 1.09–1.51). Mortality was significantly lower among statin users, including time to 30-day mortality (propensity-matched HR: 0.62, 95%CI: 0.47–0.83; propensity-adjusted HR: 0.69, 95%CI: 0.56–0.84), 14-day mortality (propensity adjusted 0.73, 95%CI: 0.57–0.93), and inpatient mortality (propensity adjusted 0.71, 95%CI: 0.56–0.89).

Conclusions: In our large national cohort study, statins were associated with significant beneficial effects on clinical outcomes among those with *S. aureus* bacteremia, including a 38% lower 30-day mortality rate among statin users compared to non-users.

625. Comparing Patient-centered Outcomes after Uterus-conserving Procedures for Uterine Fibroids Using a Linked Electronic Medical Record (EMR)-claims Database

Kristina M. Franke,[1] Aaron B. Mendelsohn,[1] Emma Brinkley,[1] Priscilla Velentgas,[1] Tongsheng Wang,[1] Evan R. Myers,[2] Kathy Lang.[1] *[1]Real-world & Late Phase Research, Quintiles, Cambridge, MA, USA; [2]Department of Obstetrics & Gynecology, Duke University Medical Center, Durham, NC, USA.*

Background: Uterine fibroids (UF) are a common cause of significant morbidity in premenopausal women. Little evidence exists on the comparative effectiveness of currently available treatments due in part to feasibility issues with RCTs and prospective observational studies.

Objectives: The aim of this study was to compare the durability of uterus-conserving treatments for symptomatic fibroids in terms of recurrent and new fibroid-related symptoms after initial surgical intervention.

Methods: We used a linked electronic medical record (EMR)-claims database with over 2.2 million patients in the USA to assemble a retrospective cohort of females aged 18–54 years with a UF diagnosis and treated with at least one procedure of interest (myomectomy, endometrial ablation, and uterine artery embolization [UAE]) occurring between 01/01/05 and 31/12/11. Time to recurrent/new symptoms after treatment was compared using proportional hazards regression adjusting for age, race, region, and number of baseline symptoms.

Results: Among 2650 women with UF, the mean age was 43 years (SD = 6.2). All patients had commercial insurance; 24% were African American, 42% were Caucasian, and 55% were from the South. The most common baseline symptoms were menorrhagia (71%) and pelvic pain (38%). Endometrial ablation was the most common index procedure (48%), followed by myomectomy (41%) and UAE (11%). Pelvic pain (43%), menorrhagia (32%), and leg pain (17%) were the most common recurring/new symptoms following index procedure. Median time to any recurrent/new symptoms was 144 days (range 1–730) for myomectomy compared to 114 for endometrial ablation (range 1–730; HR: 1.09 95%CI: 0.97–1.24) and 92 for UAE (range 1–726; HR: 1.15; 95%CI: 0.96–1.38).

Conclusions: We found that time to recurrent/new symptoms for UAE and endometrial ablation was shorter compared to myomectomy; however, the results were not statistically significant possibly due to the sample size. The collective final results from this study and future UF comparative effectiveness studies will help patients and healthcare providers make informed decisions in this therapeutic area.

626. Diabetes Treatment Intensification and Associated Changes in HbA1c and Body Mass Index

Christianne L. Roumie,[1,2] Robert A. Greevy,[1,3] Carlos G. Grijalva,[1,4] Adriana M. Hung,[1,2] Xulei Liu,[1,3] Marie R. Griffin.[1,2,4] *[1]GRECC—Geriatric Research Education Clinical Center, Veterans Health Administration-Tennessee Valley Healthcare System, Nashville, TN, USA; [2]Medicine, Vanderbilt University, Nashville, TN, USA; [3]Biostatistics, Vanderbilt University, Nashville, TN, USA; [4]Health Policy, Vanderbilt University, Nashville, TN, USA.*

Background: Despite consensus on initial diabetes treatment, when to intensify and the preferred specific treatment regimen remains unclear. Given the lack of clear recommendations for additional treatments after metformin use, and the HbA1c goals for intensification, variation in clinical practice is likely to result. Little is known about the current clinical practice patterns for patients who fail initial diabetes treatment.

Objectives: The aim of this study was to describe common type 2 diabetes treatment intensification regimens, patients' characteristics, and changes in glycated hemoglobin (HbA1c) and body mass index (BMI).

Methods: We constructed a national retrospective cohort of veterans initially treated for diabetes with either metformin or sulfonylurea from 2001 to 2008, using Veterans Health Administration (VHA) and Medicare data. Patients were followed through September 2011 to identify common diabetes treatment intensification regimens. We evaluated changes in HbA1c and BMI post-intensification for metformin-based regimens.

Results: We identified 323 857 veterans who initiated diabetes treatment. Of these, 55% initiated metformin, 43% sulfonylurea, and 2% other regimens. Fifty percent ($N = 89\,057$) of metformin initiators remained on metformin monotherapy over a median follow-up of 58 months (interquartile range [IQR] 35, 74). Among 80 725 patients who intensified metformin monotherapy, the four most common regimens were addition of sulfonylurea (79%), thiazolidinedione [TZD] (6%), or insulin (8%), and switch to insulin monotherapy (2%). Across these regimens, median HbA1c values declined from a range of 7.0–7.8% (53–62 mmol/mol) at intensification to 6.6–7.0% (49–53 mmol/mol) at 1 year and remained stable up to 3 years afterwards. Median BMI ranged between 30.5 and 32 kg/m^2 at intensification and increased very modestly in those who intensified with oral regimens but 1–2 kg/m^2 over 3 years among those who intensified with insulin-based regimens,

Conclusions: By 1-year post-intensification of metformin monotherapy, HbA1c declined in all four common intensification regimens and remained close to 7% in subsequent follow-up. BMI increased substantially for those on insulin-based regimens.

627. The Use of Low Molecular Weight Heparin and Pneumatic Compression Devises for Deep Vein Thrombosis Prophylaxis in Major Trauma Patients: A Comparative Effectiveness Analysis

Abdullah Alahmari,[1] Ziyad Almalki,[1] Guo Jeff.[1] *[1]Health Research Outcomes, University of Cincinnati, Cincinnati, OH, USA.*

Background: Venous thromboembolism (VTE) is a thrombotic disease composed of both deep vein thrombosis (DVT) and pulmonary embolism (PE). The prevalence of DVT in major trauma is 40–80%, and currently, there are different DVT prophylaxis measures; however, the optimal prophylaxis strategy for DVT in trauma patients is still controversial.

Objectives: The aim of this study was to compare the effectiveness of low molecular weight heparin (LMWH) with the pneumatic compression devices (PCDs) in the prevention of deep vein thrombosis (DVT) among major trauma patients.

Methods: A simplified decision-analysis model was established. The outcome measures for this model were the expected utilities resulting for each of the comparison categories. Our model compares two strategies, LMMW and PCDs. Patients who received LMWH will then have the chance to either develop DVT or not develop DVT. As some patients develop DVT, they have four different chances: to die, survive, survive but suffer from bleeding complications, or survive but suffer from heparin-induced thrombocytopenia (HIT). The expected utility then calculated based on the terminal node utility and probability of each possible event. PCDs patients will either develop DVT or not based on the probabilities. If developed DVT, they might die, survive, suffer from bleeding, or suffer from local tissue injury (LTI). If no DVT, they still suffer the same complications but no death due to DVT.

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Results: The LMWH strategy has a bigger expected utility comparing to that for PCDs (0.9904 vs 0.9865). The difference in the expected utility that is about 0.0039 makes the decision to choose the LMWH strategy that provides the highest possible utility. In a one-way sensitivity analysis on the probability of DVT with LMWH, PCDs were insensitive to this parameter regardless of the probability value. When the probability of DVT with LMWH is below 0.0285, then LMWH is the effective strategy. PCDs become the effective strategy when the probability of DVT with LMWH exceeds 0.0285.

Conclusions: When compared the mechanical PCDs as thromboprophylaxis with the pharmacological LMWH, LMWH is more effective.

628. Comparing Inverse Probability Weighting, Stabilized IPW and Entropy Balance Methods to Generalize Observational Cohorts to a Population

Raymond A. Harvey,[1] Jennifer D. Hayden,[1] Pravin S. Kamble,[1] Joanna C. Huang,[2] Jonathan R. Bouchard.[2] *[1]Comprehensive Health Insights, Inc., Louisville, KY, USA; [2]Health Economics and Outcomes Research, Novo Nordisk, Inc., Princeton, NJ, USA.*

Background: Inverse probability weighting (IPW) and stabilized IPW (sIPW) are methods used to control bias in observational studies, creating weights to compensate for disproportional selection probabilities. These methods are assumption dependent. In scenarios where the observed cohort (exposed) is larger than the population's target sample (unexposed), researcher post-calibration is required to achieve balance. Entropy balance (EB) calibrates weights using the target's moments as constraints, optimizing covariate balance a priori. This could be particularly useful in comparative effectiveness research.

Objectives: To determine which method effectively mitigates bias and confounding, we demonstrate covariate balance empirically and by simulation as measured by the absolute standardized mean difference (ASMD), aggregated absolute bias (AAB), and root mean square error (RMSE) and compare empirical weighted total healthcare cost estimates using IPW, sIPW, and EB.

Methods: For the simulations, four covariates (BMI, age, sex, and year) were generated creating three fictitious data sets: a population, a target, and a biased cohort to weight to the target. We address two common scenarios: the observed cohort size exceeds the target, and vice versa. The empirical application weighted a commercial health plan cohort to an NHANES target sample on the same observed covariates.

Results: EB alone achieved balance (ASMD $\leq$ 0.10) on all covariates both in simulation and empirically. In simulation, when cohort size exceeds the target, EB achieves the lowest AAB and RMSE (8.34, 30.57) compared to IPW (316.09, 316.96) and sIPW (348.09, 348.87). EB performed similarly with less magnitude in the second scenario. Empirically, only EB differed from the unweighted mean healthcare cost indicating that IPW and sIPW weighting was ineffective.

Conclusions: Entropy balance demonstrates the bias–variance tradeoff by achieving higher estimate accuracy yet lower estimate precision compared to IPW methods. Weighting with optimization methods requires no post-processing, effectively mitigating bias and confounding in both observational studies and comparative effectiveness research.

629. Improving Utility of Electronic Health Data for Clinical Research: The Need for Harmonization

Michelle Leavy,[1] Michael Barboza,[1] Estefania Rodriguez,[2] Sarah Rosenblum,[2] Lisa Green.[2] *[1]Real-world & Late Phase Research, Quintiles, Cambridge, MA, USA; [2]L&M Policy Research, Washington, DC, USA.*

Background: The use of consistently defined data elements across clinical research studies has the potential to increase opportunities for linking, comparing, and aggregating data. Many initiatives are underway to create harmonized data elements for use in research.

Objectives: The aim of this study was to identify and describe systems used to standardize language and definitions for data elements, including systems for patient registries, clinical trials, and electronic health records (EHRs).

Methods: A systematic literature review was conducted using search terms that were pilot tested for sensitivity, specificity, and feasibility. Identified publications were reviewed for relevancy using pre-determined key

words, and data were extracted into a standard abstraction form and summarized qualitatively. Additional materials were identified through discussions with a Technical Expert Panel and key informants.

Results: Many data harmonization efforts exist, ranging from efforts to define core sets of outcome measures for specific conditions to broad efforts to define data standards for EHRs. This review identified 31 efforts. Some develop data elements prospectively for use in new studies; others harmonize data elements retrospectively to support linkage or comparisons between studies. Few examples of the use of harmonized data elements in new studies and no examples documenting the actual value derived from use of harmonized data elements were found. Few examples of collaboration or shared learning across initiatives were found.

Conclusions: The potential value of harmonized data is widely understood, and significant resources are being expended to develop harmonized data elements. Sharing of lessons learned from current initiatives would benefit future efforts. Developing of case studies that describe the value derived from using harmonized data elements will also be important for increasing use. Lastly, various terms are used to describe work in this area (e.g., data standards, harmonized data elements, and common data elements), which complicates searching. Common terminology is needed to facilitate identification of harmonized data elements in the literature.

630. In Balance You Say? How We Assess Baseline Comparability in Comparative Effectiveness Research

Jin-Liern Hong,[1] Richard Wyss,[2] Til Stürmer,[1] Cynthia J. Girman.[1,3] *[1]Department of Epidemiology, Gillings Global School of Public Health, University of North Carolina, Chapel Hill, NC, USA; [2]Division of Pharmacoepidemiology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]CERobs Consulting, LLC, Chapel Hill, NC, USA.*

Background: Propensity score (PS) methods, including matching, stratification, weighting, and automated approaches, have been increasingly used to achieve baseline comparability in non-randomized comparative effectiveness research (CER) studies. However, no generally accepted metrics exist for assessing how well such methods achieve confounding control. While several have reviewed and compared balance metrics in the literature, understanding the performance of new approaches that incorporate the strength of association to outcome could be valuable.

Objectives: The aim of this study was to review approaches for assessing baseline comparability in non-randomized studies and assess performance of such approaches and balance metrics using simulated data.

Methods: A literature review identified approaches to assess balance after applying PS approaches. Graphical representations of the PS distributions by treatment are often used to examine overlap subjectively but do not show individual covariate balance. Average standardized absolute mean differences (ASAMD) are commonly used as an overall balance metric but give equal weight to all covariates. In addition, instrumental variables (IVs) could be included in its estimation, which do not need balancing since not related to outcome; including IVs in PS may increase bias in treatment effects. Lunt (2009) proposed assessing change in treatment effect estimates with and without a variable in the outcome model to assess if sufficiently balanced to control for confounding.

Results: Metrics of balance that weight covariates based on the strength of outcome association have not been used in assessing confounding control but could be useful. Standardized differences for individual covariates and ASAMD weighted according to strength of covariate–outcome association will be presented along with metrics traditionally applied (ASAMD) and Lunt's change in treatment estimates, based on simulation results.

Conclusions: ASAMD is commonly used to quantify balance between treatments in non-randomized studies but has limitations in assessing confounding control. Simulation results can quantify how different measures of balance perform in settings where degree of balance is known.

631. Best Methods to Get Your Comparative Effectiveness Paper Cited: How GRACE Helps

Nancy A. Dreyer,[1] Allison Bryant,[1] Priscilla Velentgas,[1] Zhaohui Su.[1] *[1]Real-world & Late Phase Research, Quintiles, Cambridge, MA, USA.*

Background: The GRACE checklist includes 11 questions on data and methods that can be used to evaluate

the quality of observational comparative effectiveness research (CER) studies. The checklist was developed through literature review, expert consensus, and field testing by 113 raters from five continents.

Objectives: The aim of this study was to determine which, if any, GRACE checklist questions are predictive of number of article citations and journal impact factor.

Methods: Classification and Regression Tree (CART) and multiple logistic regression analysis of GRACE checklist data collected from 56 assessments of 28 CER articles were used to identify factors predictive of number of article citations and journal impact factor.

Results: The CART analysis identified three indicators of study quality associated with a higher number of article citations. Limiting drug studies to new initiators was the single best predictor of high citations, followed by use of sensitivity analysis to quantify the influence of potential bias and the absence of immortal time bias. A separate analysis looking at the journal impact factor in the year the article was published (excluding self-citations) showed that use of sensitivity analysis was the single best predictor of high impact. In contrast, when academic and payer expert assessments of articles were used as measures of article quality, the strongest predictors of quality were use of concurrent comparator(s), similar measurement of outcomes between groups, accounting for important covariates, followed by sensitivity analyses.

Conclusions: These various examinations help identify the most important items in the GRACE checklist that can help guide high-quality observational studies of comparative effectiveness research.

632. Registry of Patient Registries (RoPR): Pilot Results and Lessons Learned for Registering Observational Studies

Michelle Leavy,[1] Daniel Campion,[1] Thomas Taylor,[2] Jannette Karl.[2] *[1]Real-world & Late Phase Research, Quintiles, Cambridge, MA, USA; [2]Global IT, Quintiles, Cambridge, MA, USA.*

Background: Patient registries generate important evidence on the effectiveness of different diagnosis and treatment options, the natural history of diseases, and treatment patterns. Until recently, information on registries was not available in a central location, making it difficult to determine the current state and potential future body of evidence.

Objectives: This study aimed to reduce redundancy, promote collaboration, and improve transparency in registry-based research.

Methods: An iterative, stakeholder-driven process was used to determine the requirements for the Registry of Patient Registries (RoPR) design and functionality. Based on stakeholder requirements, the RoPR was built as an integrated system with ClinicalTrials.gov, a well-known existing database.

Results: In 2012, the Agency for Healthcare Research and Quality (AHRQ) launched the RoPR (https://patientregistry.ahrq.gov/), the first searchable, public database of patient registries. During the pilot phase, ending in September 2013, 79 patient registries were published in the RoPR, representing 24 condition areas. Most are classified as disease/disorder/condition (44%), while others are classified as drug (16%), pregnancy (12%), and/or procedure (10%) registries. Reported registry purposes include effectiveness (21%), natural history of disease (18%), clinical practice assessment (16%), quality improvement (13%), safety or harm (9%), public health surveillance (6%), and post-marketing commitment (6%). Since the RoPR re-launch in August 2014, 38 new registries have been posted, with a similar mix of classifications and purposes.

Conclusions: Unlike other registration systems, such as the ENCePP E-Register of Studies, the RoPR relies on voluntary participation and encourages registration of a broad range of registries. As a result, the RoPR includes a diverse mix of registries, illustrating the varied ways in which registries support outcomes research. By developing a virtual community of registries, the RoPR offers a means to disseminate information on best practices and facilitate the development and implementation of core outcome measures to improve the ability of data to be linked, compared, and aggregated.

633. Epidemiology of Lactic Acidosis in Type 2 Diabetes Patients Treated with Metformin in Japan

Chia-Hsien Chang,[1] Motonobu Sakaguchi.[1] *[1]Pharmacovigilance Department, Takeda Pharmaceutical Company Limited, Osaka, Japan.*

Background: Although evidence suggests that metformin use does not result in the lactic acidosis (LA)

unless other contributing factors coexist, how such factors influence the incidence of LA is unknown in Japanese diabetic patients.

Objectives: The aim of this study was to estimate the incidences and risk factors of LA in metformin users compared to users of other anti-diabetic medications.
Methods: A cohort of 73 571 metformin users and 169 552 diabetes patients who used other diabetic medications was identified from the Japanese Medical Data Vision healthcare database managed from January 2010 to August 2014. Primary outcome was defined as incident diagnosis of lactic acidosis, accompanied with lactate test and given intravenous sodium bicarbonate or hemodialysis within 30 days. The age–sex adjusted incidence rates were conducted by Poisson regression, and the risk of lactic acidosis was determined with Cox model. All results presented as point estimate with 95% confidence interval (CI) by using SAS 9.3 software.

Results: Of a total of 31 events, 10 (32%) cases occurred in metformin users. The age–sex adjusted incidence rate in metformin users was 8.3 (95%CI, 6.00–11.4) per 100 000 person-years versus 7.4 (95% CI, 5.80–9.30) per 100 000 person-years in non-metformin users. Incidence of LA ranged from 11.8 (95%CI, 6.50–21.7) in patients with chronic liver disease to 22.9 (95%CI, 12.8–41.0) among patients with chronic kidney disease (CKD) per 100 000 person-years among metformin user. Similar rates were seen in non-metformin users for liver and/or CKD comorbidity. Use of metformin did not increase the risk of LA (adjusted hazard ratio (HR), 1.59, 95%CI, 0.72–3.49) after adjusting age, gender, the presence of complication of diabetes, CKD, chronic liver disease, heart failure, and gastric ulcer. Age (≥75 years), female, heart failure, and CKD were identified as risk factors of LA in Japanese diabetics.

Conclusions: This study found that the use of metformin did not increase the risk of lactic acidosis. It is consistent with relevant evidence that age, heart failure, and CKD are risk factors of lactic acidosis.

634. Change in Prevalence and Distribution of Diabetes Mellitus Type I and Type II Over Time in the Netherlands

Jetty A. Overbeek,[1] Fernie J. A. Penning-van Beest,[1] Eric C. J. van Dongen,[2] Ron M. C. Herings.[1]
[1]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [2]Novo Nordisk B.V., Alphen aan den Rijn, The Netherlands.

Background: As the development of diabetes mellitus (DM) type II (T2DM) is related to age and obesity, population changes over time with respect to these factors may have changed the prevalence and distribution of T1DM and T2DM in the Netherlands.

Objectives: The aim of this study was to quantify the trend in prevalence and distribution of T1DM and T2DM in the Netherlands.

Methods: Using the General Practitioner Database and the Out-patient Pharmacy Database of the PHARMO Database Network, the trend in prevalence of DM and distribution of T1DM and T2DM from 2005 to 2012 was assessed. Per year, patients with ≥2 antidiabetic drug dispensings within 6 months were selected as DM patient. Patient numbers were extrapolated to the Netherlands to determine prevalence of DM. For all patients, diabetes treatment at September 30 of that year was assessed. For patients with a GP recorded diagnosis for T1DM or T2DM, distribution of T1DM/T2DM was stratified by treatment. This distribution of DM type by treatment was applied to the treatment of patients with no GP recorded DM type to assess the distribution of T1DM/T2DM.

Results: The prevalence of DM in the Netherlands increased from 38 per 1000 males and 40 per 1000 females in 2005 to 54 per 1000 males and 52 per 1000 females in 2012. The distribution of T1DM versus T2DM among patients with DM changed from 15% versus 85% in 2005 to 8% versus 92% in 2012. Among patients with T1DM, mean (±SD) age decreased from 48 (±22) years in 2005 to 44 (±22) years in 2012. Among patients with T2DM, mean age increased from 63 (±12) years in 2005 to 67 (±12) years in 2012.

Conclusions: This study describes the epidemiology of DM in the Netherlands over 2005–2012. Prevalence of DM increased, and more patients were diagnosed with T2DM. These changes can be explained by the ageing Dutch population, better survival, more obesity and early detection of T2DM. Furthermore, introduction of the T2DM care programme in 2005 probably has led to a better registration of T2DM patients.

635. Time to Onset and Duration of Induction Therapy and Associated Factors Among Newly Diagnosed Multiple Myeloma Patients

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Akeem A Yusuf,[1,2] Tanya Bovitz,[1] Tom Matlon,[1] Winifred Werther,[3] Diana Felici,[3] Maya Mahue,[3] Kenneth Bridges,[3] Yi Peng[1]. *[1]Chronic Disease Research Group, Minneapolis, MN, United States; [2]University of Minnesota, Minneapolis, MN, United States; [3]Onyx Pharmaceuticals, an Amgen Subsidiary, South San Francisco, CA, USA.*

Background: While early start of induction chemotherapy may improve treatment outcome for patients with cancer, little is known about time to therapy onset and duration of induction therapy in newly diagnosed multiple myeloma (NDMM) patients.

Objectives: The study aimed to examine onset and duration of induction therapy and associated factors in NDMM patients in the United States.

Methods: Using Medicare 20% data, we created a cohort of adult (≥18 years) NDMM patients (2008–2010) who initiated targeted or non-targeted medications within 1 year of cancer diagnosis. Numbers of days to therapy onset and of therapy duration were examined overall and for associated factors in a univariate approach using the Kruskal–Wallis test.

Results: We identified 1455 NDMM patients. Overall, median (IQR) number of days to therapy onset from diagnosis and of therapy duration were 26 (12–64) and 195 (113–349), respectively. Neither days to onset nor duration varied significantly by age, sex, or race. Days to onset decreased from 29 to 21 days from 2008 to 2010, respectively ($p < 0.0001$), but therapy duration was similar across years ranging from 188 to 214 days ($p = 0.06$). Although days to onset were similar for patients who did (25 days) and did not (26 days) receive stem cell therapy (SCT; $p = 0.52$), median therapy duration was 25% longer at 202 days for those who did not ($p < 0.0001$). Onset was more rapid (22 vs. 38 days) and duration longer (232 vs. 140 days) for patients treated with MM-targeted chemotherapy compared with those treated with non-targeted chemotherapy, respectively ($p < 0.0001$).

Conclusions: We observed differences in time to onset and duration of induction therapy by index year, SCT status, and choice of therapy and found no demographic differences. Further studies are warranted to better understand the observed differences.

636. Prevalence and Characteristics of Patients with Low Level of Low-density Lipoprotein Cholesterol in Denmark

Sigrún AJ Schmidt,[1] Uffe Heide-Jørgensen,[1] Angelika D Manthripragada,[2] Vera Ehrenstein[1]. *[1]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [2]Amgen, Inc., Thousand Oaks, CA, USA.*

Background: With the emergence of new lipid-lowering therapies, more patients are expected to achieve substantial lowering of low-density lipoprotein cholesterol (LDL-C). However, there are limited data examining the clinical experience of patients with low (<1.3 mmol/l) or very low (<0.65 mmol/l) levels of LDL-C.

Objectives: The study aimed to identify and characterize persons with low LDL-C using data from Danish health registries.

Methods: We conducted this cross-sectional study among residents of northern Denmark. We used a clinical laboratory database to identify adults with at least one LDL-C measurement between 1998 and 2011. Based on the lowest measurement during the study period, we classified patients as having low (<1.3 mmol/l), moderate (1.3–3.3 mmol/l), or high (>3.3 mmol/l) LDL-C levels. We described their baseline demographic characteristics, entire comorbidity history, and 90-day prescription history prior to the lowest LDL-C value measured. We conducted similar analyses among individuals with very low LDL-C (<0.65 mmol/l).

Results: Among the 765 503 persons with a LDL-C measurement, 23% had high LDL-C, 73% had moderate LDL-C, and 4.8% had low LDL-C. In the latter group, 9.6% (0.46% of total) had very low LDL-C. Compared with the moderate and high LDL-C categories, patients in the low LDL-C group were more likely to be men and older and have history of cardiovascular diseases, diabetes, chronic pulmonary disease, ulcer, obesity, cancer, and use of psychotropic drugs. These patterns of distribution became even more pronounced when restricting to individuals with very low LDL-C.

Conclusions: Using population-based registries in Denmark, we identified a cohort of patients with low LDL-C and found that they differed from patients with higher LDL-C levels. These differences may be explained by various factors including prescribing patterns of lipid-lowering therapies or survival bias. The large group of persons with low LDL-C identified in this study also demonstrates the feasibility of future longitudinal studies examining background rates of cardiovascular and non-cardiovascular diseases in persons with low LDL-C.

637. Comparison of Diagnostic Accuracy of IASP Grading System and ID Pain Questionnaire in Patients with Confirmed Neuropathic Component and Chronic Low Back Pain

Kapil Gudala,[1] Dipika Bansal,[1] Babita Ghai[2]. *[1]Pharmacy Practice, National Institute of Pharmaceutical Education and Research, SAS Nagar, Punjab, India; [2]Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

Background: Diagnosis of neuropathic pain (NP) remained as a challenge to physicians due to lack of golden standard method of assessment of diagnosis of NP. Definition of NP is not clear and much debate because of its difficulty in understanding. Common methods of NP assessment have many problems.

Objectives: The aim of the study was to compare the diagnostic value of IASP grading system of NP and ID pain questionnaire with physician's assessment of NP assessment.

Methods: At baseline, patients' physician 1 (P1) had taken pain history and bedside examination and classified the patient as neuropathic, nociceptive or mixed pain conditions. Physician 2 independently assessed the patient and graded according to the IASP grading system about the certainty of NP. Researcher collected the data regarding disease details and ID pain questionnaire. The ID pain questionnaire is a self-reported symptom-based tool to assess NP which contains six items, to assess the NP. Patients scoring ≥2 for ID pain questionnaire were considered to have neuropathic component. A convenient sample of 40 patients with chronic low back pain who were diagnosed to have neuropathic component by physician were included for the analysis.

Results: As per IASP criteria, 25 (62.5%) patients were classified as definite, eight (20%) patients were classified as probable, and six patients were classified as possible, and one patient was classified as unlikely having a neuropathic component. Together, definite and probable 33 (82.5%) patients were classified as NP. As per ID pain, only 19 (47.5%) patients were classified as NP. Using IASP criteria can miss up to 13% of NP cases, whereas using ID pain questionnaire can miss up to 52% of NP cases.

Conclusions: IASP grading system has performed well in assessing NP. However, NP symptom-based screening tool, ID pain questionnaire, failed to identify about 52% of patients with clinician-diagnosed NP in patients with chronic low back pain. Thus, a careful judgement has to be taken while using this questionnaire.

638. Cross-cultural Adaptation and Validation of the Hindi Version of the Pain Catastrophizing Scale

Sreenu Lavudiya, Kapil Gudala, Dipika Bansal, Babita Ghai. *[1]Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, Punjab, India; [2]Anaesthesia, Postgraduate Institute of Medical Education and Research, Chandigarh, Punjab, India.*

Background: In patients with chronic pain, catastrophizing is a significant determinant of self-rated pain intensity and disability. The most commonly used scale to assess pain catastrophizing is pain catastrophizing scale (PCS).

Objectives: The aims of this study are to translate PCS into Hindi version and evaluate its psychometric properties in a sample with chronic low back pain (CLBP) in India.

Methods: Permission to cross culturally adapt and validate the original PCS into Hindi version was obtained from the original developer of PCS. Translation of the questionnaire was done according to standard guidelines. Face validity of translated scale was performed in a sample of 10 chronic low back patients. Validation study includes adult patients with CLBP. Baseline data including demographics, pain intensity, disability (Modified Oswestry Disability Questionnaire (MODQ)), and health-related quality of life (EQ-5D) were collected. Cross-cultural validation of the adapted Hi-PCS was then undertaken using exploratory factor analysis (principal component analysis by Kaiser criterion (eigenvalues > 1.0)), and confirmatory factor analysis using structure equation modeling was done. Concurrent validity of the scale was assessed by correlating total PCS with pain intensity, disability, and quality of life.

Results: Process of translation was successful, and results of face validity revealed a well-translated scale, Hi-PCS. A total of 100 CLBP patients were included in the study with mean Hi-PCS score of 25 (SD, 6.57). The principal component analysis revealed a three-factor model which explained 58% of the variance, such as helplessness, rumination, and magnification. Model fit indices by confirmatory factor analysis indicated a good fit. The Hi-PCS was significantly

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positively correlated with pain intensity ($r=0.651$) and MODQ ($r=0.352$) and significantly negatively correlated with the EQ-5D ($r=-0.380$).

Conclusions: This study has illustrated satisfactory psychometric properties of the Hi-PCS. It provides evidence for the validity and reliability of the Hi-PCS as an instrument for measuring pain catastrophizing in patients with chronic low back pain in Hindi-speaking country like India.

639. Trends and Outcome of Acute Poisoning in a Tertiary Care Hospital of Eastern India: A Prospective Observational Study

Suparna Chatterjee, Vivek Verma, Avijit Hazra. *Pharmacology, Institute of Postgraduate Medical Education & Research, Kolkata, West Bengal, India.*

Background: Acute poisoning is associated with high morbidity and mortality and imposes a significant burden on the healthcare system of India. However, prospective data from India are limited.

Objectives: The study aimed to generate data through prospective observational study regarding incidence, pattern and mortality profile in acute poisoning cases admitted to a tertiary care hospital of eastern India over a period of 1 year.

Methods: All diagnosed cases of acute poisoning were prospectively evaluated till death or discharge. Data related to socio-demographic background, clinical parameters, nature of suspected poison and time intervals from intake to hospital admission (primary/tertiary care) were recorded. Descriptive analysis was done and a logistic regression model constructed to identify predictors of mortality for acute poisoning by pesticides, which was the most frequent.

Results: Acute poisoning constituted 1.1% of medical emergency admissions. Out of the 198 cases, pesticides (48), sedative overdose (40) and corrosive acid poisoning (39) were the leading causes. Oral intake of poison with suicidal intent was the most commonly noted; 90% of the subjects were <30 years of age, with preponderance of males from rural background. Highest mortality (41.7%) was noted in pesticide poisoning. Multivariate analysis of death predictors in pesticide poisoning identified long time interval from poison intake to primary hospitalization as the strongest predictor (adjusted odds ratio 4.67).

Conclusions: Acute poisoning poses a significant burden in terms of both high incidence and mortality. Although complicated cases are referred to tertiary care, early referral and appropriate primary care are important to reduce this burden. Health professionals need to be aware of these issues.

640. A Multi-state Model for Investigating the Effects of Multiple Medication Use and Drug Burden Index on Transitions in Cognitive Function and Death in Community-dwelling Older Men: The CHAMP Cohort

Kris M Jamsen,[1,2] Danijela Gnjidic,[3,4] Sarah N Hilmer,[2,5,6] Jenni Ilomaki,[1] David Le Couteur,[3,6,7] Fiona M Blyth,[3,6] Vasi Naganathan,[3,6] Robert G Cumming,[3,8] J Simon Bell[1,2,9]. *[1]Centre for Medicine Use and Safety, Monash University, Parkville, Victoria, Australia; [2]Cognitive Decline Partnership Centre, Hornsby, New South Wales, Australia; [3]Centre for Education and Research on Ageing, University of Sydney, Camperdown, New South Wales, Australia; [4]Faculty of Pharmacy, University of Sydney, Camperdown, New South Wales, Australia; [5]Kolling Institute of Medical Research, St Leonards, New South Wales, Australia; [6]Sydney Medical School, University of Sydney, Camperdown, New South Wales, Australia; [7]ANZAC Institute, Concord Hospital, Concord, New South Wales, Australia; [8]Sydney School of Public Health, University of Sydney, Camperdown, New South Wales, Australia; [9]Sansom Institute, University of South Australia, Adelaide, South Australia, Australia.*

Background: In older people, it is unknown whether multiple medication use or cumulative exposure to anticholinergics and sedatives contributes to transitions in cognitive status and subsequent progression to death.

Objectives: The study aimed to investigate the effects of multiple medication use and Drug Burden Index (DBI) on transitions in cognitive function and death in community-dwelling older men.

Methods: Participants were men aged ≥70 years in Sydney, Australia. Cognitive function was assessed using the Mini-Mental State Exam (MMSE) at baseline, 2 and 5 years. The number of regular prescription medications and DBI (a measure of exposure to anticholinergics and sedatives) were collected at each wave. Data on mortality over 9 years were obtained. Multi-state modelling was used to quantify the effects of medications on transitions between MMSE 26–30

(State 1), MMSE < 26 (State 2) and, simultaneously, death. The analysis was restricted to men with English-speaking backgrounds ($n = 1059$, 862 and 611 at baseline, 2 and 5 years, respectively).

Results: There were 921 men in State 1 and 116 in State 2 at baseline. After adjustment for confounders, each additional medication used was associated with a 14% greater risk of transitioning from State 1 to death (hazard ratio [HR] 1.14; 95%CI 1.08–1.20). Every unit increase in DBI was associated with a 36% greater risk of transitioning from State 1 to death (HR 1.36; 95%CI 1.14–1.62). The HRs and CIs for the transition from State 1 to State 2 for number of medications and DBI were 0.97 (0.89–1.06) and 0.99 (0.66–1.49), respectively. The HRs and CIs for the transition from State 2 to State 1 for number of medications and DBI were 1.02 (0.91–1.15) and 1.33 (0.91–1.94), respectively. The HRs and CIs for the transition from State 2 to death for number of medications and DBI were 0.92 (0.83–1.01) and 0.76 (0.44–1.31), respectively.

Conclusions: Clinicians should exercise caution even when prescribing additional and DBI medications to older men who are not cognitively impaired.

641. Age of Initiation of Opioid Abuse Overall and by Route of Administration Among Opioid Abusers in Rural Kentucky

Angela DeVeaugh-Geiss,[1] Jennifer Havens,[2] Carl Leukefeld,[2] Paul Coplan,[1] Howard Chilcoat[1]. *[1]Purdue Pharma LP, Stamford, CT, USA; [2]University of Kentucky, Lexington, KY, USA.*

Background: A progression of opioid abuse has been described whereby users initially abuse orally and then progress to snorting or injecting. However, there are limited data available regarding initiation of specific opioid products via different routes of administration.

Objectives: The study aimed to estimate the age-of-onset distributions among a sample of individuals in rural Kentucky who abuse prescription opioids.

Methods: Structured interviews assessing opioid abuse, including the age of onset of use, were completed by 189 individuals in rural Kentucky selected for their history of abuse of original formulation OxyContin. Interviews were conducted between December 2010 and September 2011. Participants reported retrospectively about the age of initiation with each route of administration (e.g., swallowing, chewing, drinking, snorting, and injecting) for each opioid. Median age of initiation was calculated for each route and for each opioid by route of administration.

Results: The median age of the sample at the time of the interview was 32 years, and the median age of onset of any opioid abuse was 18 years. The age of onset varied by route of administration and was youngest for snorting (18 years), followed by swallowing (19 years), chewing (20 years), injecting (24 years), and drinking (27 years). The opioids with the lowest median age via each route of administration were as follows: swallowing – IR hydrocodone (20 years) and IR oxycodone (20 years); snorting – IR hydrocodone (19 years); chewing – IR hydrocodone (18 years); and injecting – generic ER oxycodone (25 years), heroin (25 years), and ER oxycodone (25.5 years).

Conclusions: IR hydrocodone had the earliest median age of onset for non-oral routes of administration (snorting, 18 years). While the median age was similar for snorting and swallowing, there was a lag between the onset of snorting and injecting prescription opioids.

642. Clinical Outcomes and Predictors in Patients with Biofilm Producing Methicillin-resistant Staphylococcus aureus (MRSA)

Diane M Gomes,[1,2] Aisling R Caffrey,[1,2] Megan K Luther,[1,2] Kerry L LaPlante[1,2]. *[1]Infectious Diseases Research Program, Providence Veteran Affairs Medical Center, Providence, RI, USA; [2]College of Pharmacy, University of Rhode Island, Kingston, RI, USA.*

Background: MRSA is a leading cause of infections and known to form biofilm. Published literature on clinical outcomes associated with biofilm producing MRSA infections or colonization is limited.

Objectives: The study aimed to identify predictors of biofilm producing MRSA infections/colonization and quantify clinical outcomes.

Methods: This retrospective study was conducted among patients with clinical MRSA isolates from the Providence VA Medical Center between 2004 and 2013 previously tested for biofilm formation. Data were collected from electronic medical records (demographics, medical, infection and medication history and laboratory and microbiology data). Clinical outcomes included mortality, MRSA reinfection, readmission,

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and MRSA-related readmission. Group differences were assessed using X^2/Fisher exact tests for categorical variables and T-test/Wilcoxon rank sum test for continuous variables. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) of the effect of biofilm producing MRSA on clinical outcomes and the identification of independent predictors.

Results: Patients with biofilm-producing MRSA (120/258, 46.5%) were significantly ($p < 0.05$) older and had a higher Charlson Comorbidity Index, used proton pump inhibitors, the presence of urinary Foley catheter, hospital admissions, surgery/procedures during admission, and shorter hospitalization. Patients with biofilm producing MRSA had a 72% lower risk of death at 90 days (adjusted OR 0.28; 95%CI 0.11–0.70) and a 2.75 times higher risk of hospitalization (adjusted OR 2.75; 95%CI 1.33–5.64) at 90 days. We were more likely to observe biofilm-producing MRSA in patients admitted to intensive care unit (ICU) (OR 2.41; 95%CI 1.11–5.21) and less likely to observe biofilm-producing MRSA in patients with a history of a diabetic ulcer/chronic wound (OR 0.16; 95%CI 0.04–0.76).

Conclusions: Though biofilms were not associated with an increased risk of mortality, patients with biofilm-producing MRSA infections/colonization were at higher risk for hospitalization within 90 days.

643. The Association of Thyroid Disorders and Incident Gout: Population-based Case-control Study

Saskia G Bruderer,[1,2] Susan S Jick,[3] Christoph R Meier,[1,2,3] Michael Bodmer[4]. *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Boston, MA, USA; [4]Division of General Internal Medicine, Bern University Hospital, Inselspital, Bern, Switzerland.*

Background: Thyroid hormones influence kidney function and thereby may alter serum urate levels, a major risk factor for gouty arthritis.

Objectives: The aim of the study was to assess the odds of developing incident gout in association with hypothyroidism and hyperthyroidism.

Methods: We conducted a retrospective population-based case-control analysis using the UK-based Clinical Practice Research Datalink (CPRD). We identified patients aged ≥18 years with incident gout between 1990 and 2010. We matched one control to each case on age, sex, general practice, calendar time, and years of active history in the database. We used conditional logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for potential confounders.

Results: Hypothyroidism was associated with an increased adjusted OR of 1.29 (95%CI 1.20–1.38) for women and 1.27 (95%CI 1.16–1.39) for men. Renal failure was an effect modifier of the association between hypothyroidism and gout (adjusted OR 1.15, 95%CI 1.08–1.23 in patients without renal failure adjusted OR 1.89, 95%CI 1.71–2.08 in patients with renal failure, respectively). Increasing age did not alter the risk of gout in association with hypothyroidism in both genders.

Hyperthyroidism was associated with an increased adjusted OR of 1.22 (95%CI 1.07–1.40) for women but not for men (adjusted OR 1.00, 95%CI 0.85–1.18). Renal failure was an effect modifier of the association between hyperthyroidism and gout (adjusted OR 1.00, 95%CI 0.89–1.12) in patients without and (adjusted OR 1.78, 95%CI 1.46–2.17) in patients with renal failure. Increasing age was associated with an increased adjusted OR of 1.47 (95%CI 1.13–1.90) in patients aged ≥80 years.

Conclusions: A history of hypothyroidism was associated with an increased OR for incident gout in both genders, while hyperthyroidism was only associated in female patients. Renal failure was a major effect modifier of the association between hypothyroidism and hyperthyroidism and gout.

644. Incidence and Prevalence of COPD by GOLD 2013 Classification in the Netherlands

Jetty A Overbeek,[1] Elsa J van den Berg,[1] Fernie JA Penning-van Beest,[1] Mona Khalid,[2] Richard Dekhuijzen,[3] Ron MC Herings[1]. *[1]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [2]Takeda Development Centre Europe Ltd, London, UK; [3]Department of Pulmonary Diseases, Radboud University Medical Centre, Nijmegen, The Netherlands.*

Background: Since 2011, a combined evaluation of spirometry, patient's symptoms, risk of exacerbations and comorbidities is recommended to classify COPD.

Information regarding the epidemiology of COPD by this classification would provide more insight into the burden of this disease.

Objectives: The study aimed to quantify the 5-year incidence (2008–2012) and 2012 prevalence of COPD in the Netherlands by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013 combined assessment categories.

Methods: Using the General Practitioners Database of the PHARMO Database Network, the 5-year incidence (2008–2012) and prevalence at 1 July 2012 of COPD (ICPC code R95) by GOLD 2013 combined assessment categories among individuals ≥40 years of age were assessed. Based on the degree of airflow limitation (using post-bronchodilator FEV1) and the risk of exacerbations (based on medication or as recorded by the GP), patients were classified as low-risk COPD (FEV1 ≥ 50% and/or ≤1 exacerbations) or high-risk COPD (FEV1 < 50% and/or ≥2 exacerbations).

Results: Using a source population of 813 800 individuals ≥40 years of age, the 5-year (2008–2012) incidence (95%CI) of COPD among patients ≥40 years of age was 0.50 (0.49–0.50) per 100 person years; this was 0.54 (0.53–0.55) among males and 0.45 (0.44–0.46) among females. The 2012 prevalence of COPD in a source population of 805, 112 individuals ≥40 years of age were 3.7 (3.6–3.7) per 100 persons; this was 4.0 (3.9–4.1) among males and 3.4 (3.3–3.4) among females. Mean (±sd) age of incident and prevalent COPD patients were 65 ± 12 and 67 ± 12 years, respectively. The distribution of low-risk COPD and high-risk COPD was 90% versus 10%. For patients treated by their GP, this distribution of low-risk and high-risk COPD was similar, while patients treated by a specialist had a distribution of 82% versus 18%.

Conclusions: This study describes the epidemiology of COPD in the Netherlands. Results on the distribution of low-risk and high-risk COPD depend on the population studied and the definitions used. Additional information on symptoms would allow a more detailed classification of patients.

645. Characteristics of Patients Enrolled in a Cancer Care Quality Program: A Linked Pharmacoepidemiology Resource in the HealthCore Research Environment

Kevin Haynes,[1] Crystal Hollick,[1] Nandini Selvam,[1] Vincent J Willey,[1] Ralph Quimbo,[1] Ozgur Tunceli,[1] Michael R Mack,[1] Jennifer Malin[2]. *[1]Research, HealthCore, Inc, Wilmington, DE, USA; [2]Anthem, Inc., Woodland Hills, CA, USA.*

Background: Clinical characteristics are lacking in administrative claims data. The Cancer Care Quality Program (CCQP), a novel program by Anthem Inc. health plans designed to align reimbursement with evidence-based, cost-effective oncology treatment, collects clinical data that can be integrated with the administrative claims data in the HealthCore Integrated Research Database (HIRD).

Objectives: The study evaluated baseline characteristics of patients within oncology practices participating in the CCQP.

Methods: Breast, colon, and lung cancer patients from practice sites participating in the CCQP were identified between 23 June 2014 and 3 December2014 (intake period). Patients were characterized based on the earliest request to utilize chemotherapy and/or supportive care medications (index date) during the intake period; analyses included patients with ≥6 months of continuous pre-index eligibility. CCQP clinical data were integrated with HIRD administrative claims data. Baseline characteristics were stratified by cancer type/stage and included pathology, biomarkers, ECOG performance status, and Deyo–Charlson Index (DCI).

Results: A total of 1230 breast, 329 colon, and 554 lung cancer patients were identified with mean(SD) ages and DCI's of 55(11), 58(10), and 62(9) and 5.7(3.2), 7.6 (2.6), and 7.7(2.8), respectively. Stage distributions indicated the greatest prevalence with stage IV disease: 38% (95%CI 36–41%), 73% (95%CI 68–78%), and 69% (95%CI 65–72%), among breast, colon, and lung cancer patients. Pathology results among lung cancer patients demonstrated 78% with non-small cell cancer. Thirty-six percent of breast cancer patients were HER2 positive, 29% of lung cancer patients were detected with EGFR mutation, and 39% of colon cancer patients were detected with KRAS mutation among those reporting test results.

Conclusions: Our analysis provides valuable insight into the clinical characteristics of CCQP patients, including stage and pathology data, of patients within participating practices. These integrated data provide comprehensive clinical characteristics for commercially insured oncology patients for future pharmacoepidemiology analysis.

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646. Iron Deficiency, Anemia and Colorectal Cancer

Cornelia Schneider,[1,2] Michael Bodmer,[1,3] Susan S Jick,[4] Christoph R Meier[1,2,4]. *[1]Basel Pharmacoepidemiology Unit, University Hospital Basel, Basel, Switzerland; [2]Department of Pharmaceutical Sciences, University Basel, Basel, Switzerland; [3]Inselspital, University Hospital Bern, Bern, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, USA.*

Background: Early detection of colorectal cancer (CRC) is critical for survival, and unexplained iron-deficiency anemia is an important symptom.

Objectives: We were interested in the prevalence and timing of anemia diagnoses and markers prior to the CRC diagnosis in the 'Clinical Practice Research Datalink' (CPRD) database.

Methods: Using the CPRD, we characterized an adult (18–89 years old) population with a CRC diagnosis between 2008 and 2012 focusing on anemia diagnoses and markers (serum ferritin (SF), hemoglobin (Hb), or mean corpuscular volume (MCV)). We identified all patients with an incident CRC diagnosis and matched the same number of patients without CRC, matching on age, sex, index date (=CRC diagnosis date), GP, and history. Using conditional logistic regression analyses, we compared the prevalence of anemia and different levels of SF, Hb, and MCV in patients with or without CRC, adjusted for potential confounders.

Results: Anemia had been diagnosed in 23% of CRC patients compared with 10% in control patients at any time prior to the index date; 14% of CRC patients had an anemia diagnosis ≤180 days prior to the CRC diagnosis. Blood tests were available for up to 80% of patients (Hb 80%, MCV 70%, SF 23%). A SF value ≤20 ng/mL was associated with a 7.06 (95% confidence interval (CI) 4.72–10.56) higher risk of CRC compared with SF values >100 ng/mL when restricted to measurements ≤180 days prior to the CRC diagnosis. For measurements done at least a year prior to the diagnosis, the odds ratio was 1.87 (95%CI 1.47–2.40). Comparing patients with Hb values <9 g/dL with patients with Hb values ≥13 g/dL, the odds ratio was 49.87 (95%CI 26.26–94.69) for measurements ≤180 days and 3.16 (95%CI 1.74–5.74) for measurements at least a year prior to the diagnosis. The corresponding odds ratios for patients with MCV values ≤80 fl compared with those for patients with MCV values >100 fl were 20.51 (95%CI 13.89–30.28) and 1.18 (95%CI 0.96–1.46), respectively.

Conclusions: The association between anemia and CRC could be confirmed; anemia diagnoses and blood markers were associated with CRC. Low levels of Hb as well as SF but not MCV were associated with a CRC diagnosis even if the measurement was ≥1 year prior to the index date.

647. Outcomes in Patients with Stable Coronary Artery Disease Post-myocardial Infarction: the HORUS Cohort Study in the French Health Insurance and Hospital-discharge Database

Patrick Blin[1,2], Caroline Dureau-Pournin[1,2], Régis Lassalle[1,2], Jérémy Jové[1,2], Florence Thomas-Delecourt[3], Cécile Droz-Perroteau[1,2], Nicolas Danchin[4], Nicholas Moore[1,5]. *[1]INSERM CIC1401, Bordeaux, France; [2]ADERA, Pessac, France; [3]AstraZeneca, Rueil-Malmaison, France; [4]European Georges Pompidou Hospital, Paris, France; [5]University of Bordeaux, Bordeaux, France.*

Background: Antiplatelet agents such as clopidogrel, prasugrel, or ticagrelor have demonstrated benefits during the first-year post-myocardial infarction (MI); long-term efficacy of ticagrelor is being assessed in the PEGASUS-TIMI 54 trial (NCT01225562).

Objectives: The HORUS study objective was to describe real-life outcomes in patients with stable coronary artery disease (SCAD) post-MI and in particular among patients similar to those included in the PEGASUS-TIMI 54 trial.

Methods: Cohort study of SCAD patients was identified by a 1-year event-free period after MI in the representative EGB French claims and hospitalisations database (2005–2010). Follow-up was at least 1 year and up to 3 years. Additional risk factors including diagnosis of diabetes, age ≥65 years, renal dysfunction, or prior MI defined high-risk patients (HRP). The PEGASUS-TIMI 54 equivalent population (PEG) was defined as HRP with age ≥50 years, without history of stroke, without end-stage renal failure, and without current use of oral anticoagulant. Outcomes were all-cause death, MI recurrence, stroke, and major bleeding. The main outcome was a composite of death, MI, or stroke. Clinical outcomes were defined by a hospitalisation in the database.

Results: A total of 2226 patients with MI were identified, including 1764 SCAD (4348 person-years (PY)), 1206 HRP (2905 PY), and 951 PEG (2314 PY). Among the SCAD, HRP, and PEG populations, 68, 61, and 61% were male, and mean (SD) age was 66 (15), 73 (12), and 74 (10) years, respectively; primary outcome rate [95%CI] was 6.5 [5.7;7.2], 8.7 [7.7;9.8], and 7.9 [6.8;9.0] per 100 PY, respectively; death 5.1 [4.5;5.8], 7.2 [6.3;8.2], and 6.5 [5.5;7.5], respectively; MI 1.1 [0.8;1.4], 1.2 [0.8;1.6], and 1.0 [0.6;1.5], respectively; stroke 0.6 [0.4;0.9], 0.8 [0.5;1.2], and 0.9 [0.5;1.2], respectively; major bleeding 1.4 [1.0;1.7], 1.7 [1.2;2.2], and 1.4 [0.9;1.9], respectively. Event rates were constant during follow-up.

Conclusions: For patients who survived 1 year after an MI, death represents the most frequent event of the composite criterion and remains substantial several years following MI.

648. Risk of Myocardial Infarction in Patients with Increased Level of Lipoprotein (A) - Retrospective Analysis of an US Insurance Claims Database and NHANES III

Tzuyung D Kou,[1] Anura Deshmukh,[1] Andres Gomez[1]. *[1]Bristol-Myers Squibb, Princeton, NJ, USA.*

Background: Early reported data from the Physicians' Health Study indicate that there is no association between lipoprotein (a) level and subsequent risk of myocardial infarction. Recent findings from Copenhagen City Heart Study suggest that elevated lipoprotein (a) levels are potentially associated with increased risk of myocardial infarction (MI). Risk estimates in previous studies did not adequately control for baseline patient characteristics such as cardiovascular risk factors or other laboratory findings.

Objectives: This retrospective analysis estimated the risk of MI in patients with elevated Lp(a) levels using records from a large US insurance claims database.

Methods: A total of 25 624 men and women in a US insurance claims database from 2003 to 2012 with laboratory findings of lipoprotein (a) and LDL or HDL were included in the study cohort. Patient demographic and history of cardiovascular disease or MI were captured at baseline. Risk of MI was estimated using multivariate Cox regression. Concomitant statin use was documented. NHANES III survey findings were referenced to provide population estimates.

Results: Patients with Lp(a) level greater than 200 nmol/l had higher prevalence of heart disease (26.9%) and statin use (14.8%), compared with patients with lower Lp(a) levels. Patients with concomitant statin use had comparable MI risks across Lp(a) levels (adjusted HR = 0.70, 95%CI: 0.39–1.26 to HR = 0.85, 95%CI: 0.51–1.39). In patients with concomitant statin use, those with Lp(A) ≥200 nmol/l had higher risk of MI 1.46 (1.13–1.89) compared with those with lower levels, representing 0.86 of the total US population.

Conclusions: This retrospective analysis of patients demonstrated a stepwise increase in risk of MI with increasing levels of lipoprotein (a). Specifically, concomitant use of statin appears to attenuate the risk of MI across different Lp(a) levels, while patients with higher levels of Lp(a) and no concomitant statin treatment had higher risk of MI. Findings from this study further clarify the role of Lp(a) levels in the context of statin use.

649. Subgroups of Depression in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study: A Latent Class Analysis

Christine M Ulbricht,[1] Anthony J Rothschild,[2] Kate L Lapane[1]. *[1]Clinical and Population Health Research Program, Department of Quantitative Health Sciences, University of Massachusetts Medical School, Worcester, MA, USA; [2]Center for Psychopharmacologic Research and Treatment, Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA.*

Background: Major depression varies widely. This is likely partially explained by non-specific symptomatology and variability in severity and trajectory of depression. Understanding this heterogeneity and delineating subgroups of depression is necessary to identify predictors of response and ultimately to provide precision medicine for depression.

Objectives: The study aimed to characterize the subtypes of major depression, evaluate gender differences in subtypes, and examine sociodemographic and clinical correlates of each subtype.

Methods: Latent class analysis was applied to baseline data from 2861 participants in Level 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Individual DSM-IV criterion symptoms for major depression from the Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$)

were used as indicators of the latent depression subtype variable. Multinomial logistic models identified the correlates of latent classes (adjusted odds ratios (aOR) and 95% confidence intervals (CI)).

Results: Four latent classes were identified: mild (women: 38%, men: 27%, $p < 0.01$), moderate (women: 20%, men: 24%, $p = 0.10$), severe with increased appetite (men: 12%, women: 22%, $p < 0.01$), and severe with insomnia (women: 31%, men: 26%, $p = 0.01$). Comorbid generalized anxiety disorder (aOR_{women}: 1.74; 95%CI: 1.06–2.85), bulimia (aOR_{women}: 5.44; 95%CI: 3.28–9.03; aOR_{men}: 12.60; 95%CI: 5.40–29.43), and social phobia (aOR_{women}: 3.70; 95%CI: 2.36–5.80; aOR_{men}: 3.29; 95%CI: 1.74–6.23) were correlated with severe with increased appetite. Generalized anxiety disorder (aOR_{women}: 2.89; 95%CI: 1.91–4.39; aOR_{men}: 2.05; 95%CI: 1.22–3.42), post-traumatic stress disorder (aOR_{women}: 2.29; 95%CI: 1.50–3.49; aOR_{men}: 1.94; 95%CI: 1.20–3.13), and social phobia (aOR_{women}: 2.43; 95%CI: 1.61–6.67) were correlated with severe with insomnia.

Conclusions: Insomnia and increased appetite distinguished the subtypes of depression. Anxiety disorders and other psychiatric comorbidities also differed between subtypes. These results suggest that sleep disturbances, metabolic changes, and other mental disorders may play a role in the etiology and treatment of depression.

650. Body Mass Index and Risk of Dementia in a Cohort Study of Two Million People in UK Primary Care Database

Nawab Qizilbash,[1] John Gregson,[2] Michelle E Johnson,[1] Neil Pearce,[2] Ian Douglas,[2] Kevin Wing,[2] Stephen JW Evans,[2] Stuart J Pocock[2]. *[1]OXON Epidemiology, London, UK; [2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK.*

Background: Dementia and obesity are huge public health issues, and it has been proposed that obesity in middle age may lead to dementia in old age.

Objectives: The study aimed to investigate the association between body mass index (BMI) and risk of dementia.

Methods: This was a cohort study using routine UK primary care data from the Clinical Practice Research Datalink (CPRD). The study population included people aged 40 years or older with a first BMI recording between 1992 and 2007. Follow-up was from first eligible BMI reading until the first record of dementia with censoring at earliest of practice's last data collection date and patient death/transfer out of practice. People with a prior record of dementia were excluded. Incidence rates were calculated for each BMI category using Poisson regression.

Results: The study population included 1 958 191 people in UK general practices with a mean baseline age of 56 years and a median follow-up of 9.1 years. Dementia occurred in 45 507 people, a rate of 2.4 per 1000 person years. Age and sex standardised rates per 1000 person years were 3.6 for underweight (95%CI 3.5–3.8), 2.7 for normal weight (95%CI 2.7–2.8), 2.2 for overweight (95%CI 2.2–2.3), 2.1 for obese class I (95%CI 2.0–2.1), 2.0 for obese class II (95%CI 1.9–2.1) and 1.9 for obese class III (95%CI 1.8–2.1). Compared with normal weight people, those underweight (BMI $<20\,kg/m^2$) had a 34% excess risk of dementia (95% CI 29–38%). The dementia risk decreased for every increasing BMI category: from overweight (BMI 25–29.9 kg/m^2) with 18% lower risk (95%CI 16–20%) to very obese (BMI $>40\,kg/m^2$) with 29% lower risk (95%CI 22–36%). These patterns persisted throughout two decades of follow-up, after adjustment for potential confounders and allowance for the J-shape of BMI with mortality.

Conclusions: Being underweight in middle and old age carries an increased risk of dementia over two decades. Our findings are contrary to the hypothesis that obesity in middle age may increase the risk of dementia in old age. The reasons for and public health consequences of these findings require further investigation. There may be implications for drug development for prevention of dementia.

651. The Prevalence of Sjögren's Syndrome in United States Health Insurance Claims

Susan A Hall,[1] Maneesh Juneja,[1] Lisa Vinikoor,[1] Cristina Musselli,[1] Nathalie Franchimont[1]. *[1]Biogen Idec, Cambridge, MA, USA.*

Background: In the U.S., the epidemiology of Sjögren's syndrome (SjS) is poorly understood.

Objectives: To increase the evidence base, we conducted a study of SjS prevalence and patient characteristics in a

large database of health insurance claims, the Clinformatics Data Mart Multiplan™.

Methods: The data resource contains approximately 100 million persons with health insurance coverage in the U.S. from nine census regions, primarily from commercial insurance plans. Data years 2004 to 2012 quarter 1 were used in this study. SjS was defined as ≥2 ICD-9 medical service dates with codes of 710.2 (sicca syndrome). The first occurrence of 710.2 was assigned as the index date. Pharmacy medication dispensings were described using Uniform System of Classification Level 2 National Drug Code groupings in a subset of 23 235 SjS cases with pharmacy benefits during 12 months post-index date. To better understand the epidemiology of primary SjS (pSjS), in a secondary case definition, we excluded patients with a prior service date for any ICD-9 code for systemic lupus erythematosus (710.0), rheumatoid arthritis (714. X), or scleroderma (710.1) that occurred on or before the SjS index date.

Results: A total of 53 381 persons met the SjS case definition; 90.3% were female, and the median and mean age at index date was 53.0 and 51.3 (standard deviation: 12.1), respectively. The crude prevalence of SjS was 0.06%. Among medications dispensed to SjS cases, anti-infectives (broad/medium spectrum) were most frequently noted (61.3%), followed by hormone/corticoids (plain) (42.4%) and narcotic analgesics (39.2%); 23.9% were dispensed ophthalmologic anti-inflammatories; 64.6% ($N = 34{,}473$) of SjS cases met the pSjS case definition, resulting in a crude prevalence of 0.04% for pSjS.

Conclusions: Our prevalence estimates for SjS and pSjS were in the range of previous studies that used ICD-9 codes to define disease state (0.016% to 0.147%). To our knowledge, this is the first study of SjS prevalence in U.S. health claims.

652. Factors Associated with Primary and Secondary Diagnosis of Clostridium Difficile Infection

Robert McConeghy,[1] Cynthia Willey,[1] Aisling Caffrey[1,2]. [1]*Pharmacy Practice, University of Rhode Island College of Pharmacy, Kingston, RI, USA;* [2]*Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, USA.*

Background: Clostridium difficile is gram-positive bacteria which can infect the colon, causing severe diarrhea and life-threatening colitis. Clostridium difficile infection (CDI) increases length of stay, costs, and mortality in vulnerable hospitalized populations.

Objectives: The aim was to investigate the risk factors associated with primary and secondary diagnosis of CDI.

Methods: A case-control study was performed using the 2009 National Inpatient Sample, a 20% stratified sample of US community hospitals. Independent predictors of a secondary CDI diagnosis, as compared to a primary diagnosis, were identified from logistic regression models.

Results: Our study included 7444 patients with a secondary diagnosis and 21 819 patients with a primary diagnosis. The odds of a secondary diagnosis was higher for Asian Americans (odds ratio [OR] = 1.78, $p < 0.01$), Hispanics (OR = 1.15, $p < 0.01$), and African Americans (OR = 1.16, $p < 0.01$) relative to whites. Relative to the young (age < 18 years), the odds of a secondary CDI diagnosis was lower among the middle aged (40–60 years) and older patients (60+ years) (OR = 0.56, $p < 0.01$).

Numerous comorbidities were associated with a primary diagnosis of CDI ($p < 0.05$): AIDS (OR = 0.12), electrolyte disorders (OR = 0.34), weight loss (OR = 0.62), renal failure (OR = 0.62), metastatic cancer (OR = 0.64), lymphoma (OR = 0.69), congestive heart failure (OR = 0.75), liver disease (OR = 0.78), pulmonary circulation diseases (OR = 0.79), hypertension (OR = 0.80), solid tumor (OR = 0.83), pulmonary disease (OR = 0.85), and valvular disease (OR = 0.85). The only comorbidity predictive of a secondary diagnosis of CDI was alcoholism (OR = 1.24).

Conclusions: In this large, nationally representative population of seven million inpatients, younger, nonwhite inpatients had a higher likelihood of a secondary CDI diagnosis, as did those with a diagnosis of alcoholism. Patients with comorbidities, which suggest prior hospitalizations, were more likely to present with a primary CDI diagnosis. This relationship should be further explored in longitudinal studies. These cross-sectional data document differences may be helpful for identifying inpatients with a predisposition toward primary CDI.

653. Incidence of Pulmonary Embolism Among Postmenopausal (PM) Women with ER+/HER2− Breast Cancer

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Xiaofeng Zhou,[1] Cynthia de Luise,[1] Rongjun Shen,[1] Andrew Bate,[1] Nicolle Gatto[1]. [1]*Epidemiology, Pfizer Inc, New York, NY, USA.*

Background: Estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2−) breast cancer (BC) is the most common subtype of BC. While malignancy increases the risk of pulmonary embolism (PE), data on PE incidence in PM women with ER+/HER2− BC is lacking.

Objectives: The study aimed to estimate the incidence rate (IR) of PE among PM women with ER+/HER2− BC, stratified by advanced (metastatic) vs. non-advanced BC.

Methods: A retrospective cohort study using 2007–2013 Humedica data, a US EMR database. ICD-9, NDC codes, and unstructured data were used to identify cohorts and PE. Females aged 55+ or >18 years (yrs) when first exposed to letrozole with ≥6 months of enrollment, no PE history before first diagnosis of ER+/HER2- BC, and met the inclusion/exclusion criteria were included. Three cohorts were created: (1) advanced ER+/HER2− BC; (2) non-advanced ER+/HER2− BC; and (3) PM women ≥55 yrs with non-cancer.

Results: A total of 1460 advanced and 6758 non-advanced ER+/HER2− BC and 1 737 584 non-cancer PM women were identified. Mean age was 65–67 yrs. across three cohorts. Most women were White: ≥85% in BC cohorts and 70% in non-cancer cohort. The crude IRs of PE in cohorts 1, 2, and 3 were 1.9 (95%CI: 1.5–2.5), 0.8 (95%CI: 0.7–1.0), and 0.2 (95%CI: 0.2–0.2) per 100 person years (PY), respectively, with a crude IR ratio (IRR) of 2.4 (95%CI: 2.3–2.5) for cohort 1 vs. 2 and 8.0 (95%CI: 7.6–8.4) for cohort 1 vs. 3. The crude IRs were higher with older age (65+ vs. <65 yrs) with crude IRR of 1.5 (95%CI: 1.4–1.7), 1.7 (95%CI: 1.6–1.8), and 2.2 (95%CI: 2.2–2.2) and in African Americans (AA vs. White) with crude IRR of 1.2 (95%CI: 1.0–1.4), 3.1 (95%CI: 2.8–3.3), and 1.5 (95%CI: 1.5–1.5), for cohorts 1, 2, and 3, respectively. AA <65 yrs with advanced ER+/HER2− BC had highest crude IR of 2.8 (95%CI: 0.9–8.8) per 100 PY.

Conclusions: We found that advanced ER+/HER2− BC confers an unadjusted >two-fold and eight-fold greater risk of PE compared with non-advanced ER+/HER2− BC and non-cancer, respectively. This study adds important data on the risk of PE among PM patients with ER+/HER2− BC. Future analyses may benefit from confounder adjustment, medical chart review, and estimation using other databases.

654. Minimally Important Differences for Patient-reported Outcomes Measurement Information System (Promis) Fatigue and Pain Interference Scores

Jennifer Beaumont,[1] James F Fries,[2] Jeffrey R Curtis,[3] David Cella,[1] Huifeng Yun[3]. [1]*Northwestern University Feinberg School of Medicine, Chicago, IL, USA;* [2]*Stanford University School of Medicine, Stanford, CA, USA;* [3]*Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA.*

Background: Interpretation of patient-reported outcomes (PROs) requires some definition of an important or meaningful difference.

Objectives: This study aimed to estimate minimally important differences (MIDs) for the Patient-reported Outcomes Measurement Information System (PROMIS®) Fatigue and Pain Interference scale scores in rheumatoid arthritis (RA).

Methods: The responsiveness of several PROs was assessed in an observational cohort of 521 RA patients in the Arthritis, Rheumatism and Aging Medical Information Systems (ARAMIS) cohorts. PROMIS Fatigue and Pain Interference instruments were administered at baseline, 6 and 12 months. Self-reported retrospective changes in fatigue and pain over the previous 6 months were obtained at the follow-ups (a lot better/worse, a little better/worse, stayed the same). We estimated MIDs using the mean change in PROMIS scores for people who rated their change 'a little better' or 'a little worse.'

Results: At 6 months, 41 patients reported their fatigue was a little better compared to baseline (mean change [SD]: −2.6 [4.8]), 119 a little worse (1.7 [5.6]). Pain was a little better for 60 patients (−1.9 [6.1]) and a little worse for 126 (0.6 [5.7]). At 12 months, fatigue was a little better compared to 6 months prior for 31 patients (−1.3 [6.5]) and a little worse for 133 (0.9 [5.6]). Pain was a little better for 53 patients (−1.8 [5.7]) and a little worse for 122 (1.5 [5.0]). Thus, the MID range was 1–2 points for both Fatigue and Pain Interference. Correlations between change scores and retrospective ratings were

low (0.13–0.29), indicating that these analyses may underestimate the MID.

Conclusions: The MID for PROMIS Fatigue and PROMIS Pain Interference, estimated from this cohort of RA patients, is roughly 2 points and corresponds to a small effect size. This is consistent with earlier work in this cohort demonstrating an MID of 2 points for PROMIS Physical Functioning.

655. Attention Deficit Hyperactivity Disorder (ADHD) and Socioeconomic Status in Children and Adolescents in the UK

Adrian J Hire,[1] Darren M Ashcroft,[1] David A Springate,[2] Doug Steinke[1]. *[1]Centre for Pharmacoepidemiology and Drug Safety, Manchester Pharmacy School, University of Manchester, Manchester, UK; [2]Institute of Population Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK.*

Background: Research has suggested that an individual's chance of being diagnosed with ADHD may be influenced by his or her socioeconomic status. Prescription analysis has identified geographical variations in spending for ADHD in England; it is unclear if this is associated with regional variations in diagnostic rates and deprivation levels.

Objectives: This study aimed to assess the geographical distribution of ADHD in the UK and discern if there were differences in diagnostic rates between regions. It also examined if there was an association between ADHD and socioeconomic deprivation on a national scale.

Methods: The study used data from the Clinical Practice Research Datalink (CPRD). The study population comprised patients diagnosed with ADHD before the age of 19 years, between 1 January 2004 and 31 December 2013. Patients with a diagnosis of ADHD were identified by the presence of codes relating to the disorder in their medical records. Using CPRD data, patients were stratified according to the region in which their general practice was based. Each practice has an Index of Multiple Deprivation (IMD) score based on the locality in which it is sited; this relative measure of deprivation provided a surrogate measure of patients' deprivation status.

Results: Between 2004 and 2013, there were 10 284 new diagnoses of ADHD. Most patients were diagnosed between the ages of 7 and 12 years (56.67%, $n = 5828$), and 81.75% ($n = 8407$) of those diagnosed were male. The South East England region had the highest incidence of ADHD [1.59 cases per 1000 person-years at risk/PY (95%CI 1.51–1.67). Yorkshire had the lowest incidence of ADHD [0.81 cases per 1000 PY (95%CI 0.71–0.93)]. There appeared to be a linear association between socioeconomic deprivation and ADHD incidence in England. In the other three nations of the UK, evidence for an association was somewhat weaker.

Conclusions: There were notable differences in ADHD incidence between UK regions. In England, incidence of diagnosed ADHD was highest amongst the most deprived patients and lowest in patients from the least deprived areas.

656. Does FEV_1 Change Predict Hospital Admission and All-cause Mortality in Patients with Chronic Obstructive Pulmonary Disease (COPD)?

Robert W Flynn,[1] Thomas M MacDonald,[1] Adrian Hapca,[1] Isla S Mackenzie,[1] Li Wei,[2] Steve V Morant,[1] Stuart Schembri[1]. *[1]Medicines Monitoring Unit, University of Dundee, Dundee, UK; [2]UCL School of Pharmacy, University College London, London, UK.*

Background: Forced expiratory volume in the first second (FEV_1) is an integral part of COPD diagnosis and an important prognostic indicator. However, it is only weakly correlated with breathlessness and other markers of disease progression. We hypothesised that rate of decline in FEV_1 might be a better marker of disease progression.

Objectives: The study aimed to investigate whether there is an association between the rate of change of FEV_1 and respiratory morbidity or mortality in COPD patients.

Methods: This was a cohort study of COPD patients in Tayside, Scotland, from February 2001 to March 2012. Patients were clinically evaluated annually, and their spirometry was entered into a managed clinical database. Patients were included if they had FEV_1 measured on two or more occasions. Outcomes were record-linked from hospitalisation, mortality and prescribing data. The primary outcome was hospitalisation for respiratory disease (ICD10 codes: J10–J12, J15–J18, J44–J45). Other outcomes were

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all-cause mortality and prescribed oral steroids, a surrogate of COPD exacerbation. FEV_1 between consecutive visits was expressed as percentage change between the two. Generalised estimating equations (GEEs) were used to calculate multivariate associations between change in FEV_1 and outcomes. FEV_1 change was analysed as a time-dependent variable with potentially confounding covariates evaluated at baseline. All analyses were done in SAS v9.2.

Results: A total of 2881 patients had a total of 8588 visit pairs. There were 907 hospital admissions, 250 deaths and 7761 courses of prescribed oral corticosteroid. There was no association between rate of change of FEV_1 and any of the outcomes: RR 1.00 (95%CI 0.95–1.05), 0.93 (0.82–1.06), 0.99 (0.96–1.01), respectively. In an exploratory analysis, we found that the absolute rate of change in FEV_1 (the change ignoring whether an increase or a decrease) was positively associated with risk of hospitalisation.

Conclusions: We found no evidence that the change in FEV_1 was associated with any of the outcomes used in the study (hospitalisations, mortality or prescribing of oral corticosteroids). However, absolute rate of change in FEV_1 was associated with worse outcomes.

657. Correlates of Patient Delay in the Initiation of Treatment Among New Smear-positive TB Patients in Rural Health Settings in the Philippines

Imelda G Pena.[1] [1]*Pharmacy, University of the Philippines Manila, Manila, Philippines.*

Background: Despite the National TB Control Program, Philippines remained to be a high TB-burden country. Caloocan City, the third largest city in the Philippines, had several TB symptomatics who presented themselves to the health facility with delay. The delay in start of treatment eventually led to increased risk of transmission of the disease, increased severity of disease leading to death, and increased costs of TB care for patients and for the society. Patient delay is defined as the duration of time (in days) from 21 days after onset of TB symptoms until first visit to a health facility.

Objectives: The study aims to determine the proportion, duration, and correlates of patient delay in the initiation of treatment among new smear-positive TB patients in rural health settings in the Philippines.

Methods: A cohort of 456 adult patients (15 years old) diagnosed as new smear-positive TB patients who initiated TB treatment within the past 2 weeks to 1 month in 40 Rural Health Units in Caloocan City was included. Each patient was invited to participate through the signed informed consent form. Interview-guided pre-tested questionnaire was used in obtaining data on socio-economic, psychosocial, and health facility-related variables. Descriptive and inferential analyses were conducted, including crude, stratified, and multiple logistic regression analyses.

Results: Analyses revealed that patients with moderate to high fear or stigma were twice more likely to have patient delay than those without fear or stigma (OR = 1.81, 90%CI: 1.13–2.91, $p = 0.038$). Further, respondents who had poor level of awareness of TB symptoms were 1.5 times more likely to demonstrate patient delay than those with good or moderate awareness (OR = 1.45, 90%CI: 0.999–2.109, $p = 0.101$).

Conclusions: It is hoped that public health interventions would target patients who may be potential delayed health seekers in the community, including those with high stigma to TB and with poor awareness of TB symptoms. Health education efforts should be strengthened to increase public awareness of the utilization of health care services at the public and private sectors.

658. Breast Cancer Subtype and Survival in a Population-based Cohort of Patients from California

Christina A Clarke,[1] Scarlett Lin-Gomez,[1] Li Tao,[1] Lisa Moy,[1] Juan Yang,[1] Lisa I Wang,[2] Mary S Beattie,[2] Jennifer Eng-Wong,[2] Melissa Brammer,[2] Laura Chu[2]. [1]*Cancer Prevention Institute of California, Fremont, CA, USA;* [2]*Genentech, Inc, South San Francisco, CA, USA.*

Background: BC is a heterogeneous disease comprising distinct subtypes defined at present by tumor molecular markers. More effective treatments targeted to specific markers have been developed in clinical trials. Little is known about survival patterns associated with specific subtypes in the general population.

Objectives: We examined overall survival outcomes according to tumor subtype and stage in a diverse, population-based cohort of BC patients (pts) in California.

Methods: In California (CA) Cancer Registry, we identified all female CA residents diagnosed with primary

invasive BC between 1 January 2005 and 31 December 2011. We classified these cancers as early BC (EBC, stages I–III) vs. *de novo* metastatic (MBC, stage IV). We further grouped these cancers into four subtypes based on HER2 and hormone receptor (HR) status. For a subset of women with available survival data, we calculated the proportion surviving at 3 years (yrs) and median overall survival using the Kaplan–Meier method.

Results: A total of 118 817 EBC pts (61.4% HR+/HER2−, 9.9% HR+/HER2+, 13.3% unclassified, 4.9% HR−/HER2+, and 10.6% triple negative (TN)) and 6268 MBC pts (43.7% HR+/HER2−, 13.0% HR+/HER2+, 23.3% unclassified, 8.9% HR−/HER2+, and 10.7% TN) were identified. For EBC, 3-yr survival rate was highest (95.1%) for HR+/HER2− pts and shortest (84.3%) for TN. For the HER2− and HER2+ overall groups (regardless of HR status), 3-yr survival was similar (93.3% vs. 92.5%, respectively). The longest survival for *de novo* MBC was observed for the HR+/HER2+ subtype (median OS: 45.3 months (mos)), compared with 38.7 mos for the HR+/HER2− subtype, 23.1 mos for the HR−/HER2+ subtype, and 12.7 mos for the TN subtype. For the overall HER2+ and HER2− subtypes, HER2+ MBC had slightly better survival (3-yr rate: 47.6%, and median OS: 33.6 mos) than HER2− MBC pts (3-yr rate: 44.8%, and median OS: 30.9 mos).

Conclusions: This study demonstrates the relevance of subtype on the OS of BC pts in a large population of CA women. Although HER2+ status is a negative prognostic factor, survival was similar between HER2+ and HER2− pts, likely due to available treatments targeting HER2. TNBC pts had the shortest survival, especially for metastatic disease.

659. Cardiovascular and Renal Morbidity in Gout Patients in Germany, United Kingdom, United States, and France

Fredrik Nyberg,[1] Javier Nuevo,[2] Laura Horne,[3] Robert Morlock,[4] Chris Storgard,[4] Lalitha Aiyer,[4] Dionne M Hines,[5] Xavier Ansalobehere,[6] Pierre Chevalier[7]. *[1]AstraZeneca, Mölndal, Sweden; [2]AstraZeneca, Madrid, Spain; [3]AstraZeneca, Wilmington, DE, USA; [4]Ardea Biosciences, San Diego, CA, USA; [5]IMS Health, Alexandria, VA, USA; [6]IMS Health, Paris, France; [7]IMS Health, Vilvoorde, Belgium.*

Background: Gout is a metabolic condition that in most patients results from inadequate uric acid excretion, leading to hyperuricemia and deposition of urate crystals in tissues of the body. Patients typically have low health status, and comorbidities such as chronic renal impairment and cardiovascular (CV) diseases are common.

Objectives: The study aimed to estimate prevalence and incidence rates (IRs) of renal and CV morbidities in gout patients in Germany (DE), United Kingdom (UK), United States (US), and France (FR).

Methods: A longitudinal cohort study from 1 January 2009 to 31 December 2011 was conducted using data from IMS' Disease Analyzer™ (DE and FR) and PharMetrics Plus linked to outpatient lab data (US), and CPRD-HES (UK). Patients were required to have "prevalent established gout" (treated with urate-lowering treatment [ULT] or eligible for ULT per ACR guidelines) between 1 January 2009 and 31 December 2009, age ≥18 years on index date (1 January 2010) and ≥1 visit both before 1 January 2009 and after 1 January 2010. Follow-up for incident events extended from index to 31 December 2011 (all dates +1 year for FR). Events of interest were identified based on diagnostic codes/lab data.

Results: A total of 35 188 (DE), 17 388 (FR), 121 591 (US), and 24 607 (UK) patients were analyzed. Among the baseline renal conditions, abnormal serum creatinine was the most prevalent in the UK (30.6%); diagnosis of CKD/renal failure was most prevalent in the UK (10.9%) and DE (6.7%). Hypertension (HTN) was the most prevalent CV diagnosis in all four countries (59.5% [DE], 31.2% [FR], 52.4% [US], and 24.4% [UK]), followed by ischemic heart disease (IHD) and myocardial infarction (MI). IRs (per 100 patient-years) for new/worsening renal impairment ranged from 1.7 (DE) to 4.3 (US) and for nephrolithiasis diagnosis from 0.31 (FR) to 3.8 (US). Among CV conditions, IR of HTN diagnosis was the highest, from 3.2 (UK) to 20.3 (US), followed by IHD (range 0.53 [FR] to 2.73 [DE]); MI ranged from 0.13 [FR] to 1.01 [US].

Conclusions: Gout patients frequently have comorbid renal and CV disease and are at risk for new events, which increases disease burden in this population. Awareness and consideration of these comorbidities are important in the medical management of gout patients.

660. Trends in Healthcare Utilization and Cost of Epilepsy Across Ages 0–90 years

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Chintan Dave,[1] Abraham Hartzema[1]. [1]*Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA.*

Background: There is a paucity of information on the trends in healthcare utilization and costs of epileptic patients over changes in age.

Objectives: The study aimed to describe the healthcare utilization trends and cost of illness for epilepsy in ages 0–90 years

Methods: Medicaid Analytic eXtract (MAX) data from 29 states, Marketscan Commercial Claims and Marketscan Medicare claims, from 2008 to 2010 were utilized for this study. MAX data for patients were limited to patients aged 0–18 years. Due to data heterogeneity, we implemented different inclusion and exclusion criteria. We used only claims data for Medicaid and utilized both claims and encounter data for Marketscan. We identified epileptics as those with two ICD9 codes for epilepsy 30 days apart but within 180 days. For the primary analysis, we calculated total costs attributable to epilepsy (TEC), percentage contribution of epilepsy related inpatient (IPP), outpatient (OTP), and prescription costs (RXP) to overall epilepsy costs, and percentage contribution of epilepsy-related costs to overall healthcare costs (ECP). All costs were adjusted to 2010 dollars using healthcare inflation. Additional sensitivity analysis was also conducted using epilepsy subtypes.

Results: We examined healthcare records for 452 354 epilepsy patients (202 550 from Medicaid, 227 515 from Marketscan commercial, and 22 273 from Marketscan Medicare). For ages 0–18 years, we found similar cost trends between Medicaid and Marketscan, except in ECP. ECP costs were lower in Medicaid compared with Marketscan, implying Medicaid recipients have more comorbid conditions. ECP was 60% at the beginning of life and consistently decreased as age increased until reaching 32% at the age of 90 years. OTP was consistently around 40% in all the age groups. IPC was highest in the first year of life at 60% but decreased dramatically to a nadir of 12% at the age of 16 years and increased consistently reaching 32% at the age of 90 years. Surprisingly, TEC decreased consistently as the age increased.

Conclusions: We found the healthcare utilization and costs of illness to be strongly related to age. Identification of these trends could lead to better understanding on how patients consume healthcare resources over age.

661. Non-medical Use of Benzodiazepines and Opioids: An Online National Survey in the United Kingdom

Jody L Green,[1] Andrea C Besharat,[1] Erin M Goodman,[1] Becki Bucher-Bartelson,[1] David M Wood,[2] Paul I Dargan.[2] [1]*Research, Rocky Mountain Poison and Drug Center, Denver, CO, USA;* [2]*Clinical Toxicology, Guy's and St. Thomas' NHS Foundation Trust and King's Health Partners, London, England, UK.*

Background: Data on poly-drug use and non-medical use (NMU) of prescription drugs in Europe are limited; this is important given the high prevalence of prescription drug abuse in the United States.

Objectives: The study aimed to report use and NMU of opioids only, benzodiazepines only, and opioids and benzodiazepines (both) in a United Kingdom (UK) national survey.

Methods: An online cross-sectional study was undertaken in July 2014. Respondents were obtained from a panel maintained by a market research company. Those aged 16 years and older living in the UK were eligible. The 2504 respondents reflect the geographical and gender distribution of the UK. Respondents were excluded if they reported use of all illicit drugs in the last 7 days or NMU of all opioids ($n=5$). Lifetime use and NMU of prescription drugs (use without doctor's prescription or for any reason other than recommended by a doctor), illicit drug use, chronic pain (pain lasting at least 3 months that occurs constantly or flares up frequently), and Drug Abuse Screening Test (DAST-10) were analyzed. Chi-square tests and Kruskal–Wallis for statistical differences were performed.

Results: A total of 2499 respondents completed eligible surveys; 1509 (60.4%) reported opioid use only, 31 (1.2%) benzodiazepine use only, and 412 (16.5%) use of both. Of the 979 (39.2%) respondents reporting NMU of an opioid or benzodiazepine, most (94.2%) reported NMU of opioids only. However, 80.7% of those reporting NMU of benzodiazepines also reported NMU of opioids (19.3% reported NMU of benzodiazepines only). Respondents reporting NMU of both had the highest proportion of chronic pain (69.6%, $p=0.0045$) and illicit drug use (71.7%, $p<0.0001$) and the highest median DAST-10 (3.0, $p<0.0001$) compared with the opioids or benzodiazepine groups.

Conclusions: These data suggest high prevalence of NMU of opioids in the UK, although the prevalence of NMU of benzodiazepines was lower. Amongst those reporting lifetime NMU of benzodiazepines, opioids were often also reported. This study confirmed poly-drug NMU may indicate severe health consequences related to drug abuse. Understanding poly-drug NMU is important to inform interventions.

662. Primary Sclerosing Cholangitis in the UK Clinical Practice Research Datalink (CPRD GOLD)

Huifang Liang,[1] Jennifer H Lin,[1] Jesse Shick,[1] Sudhakar Manne,[1] Punam Bharania,[2] Paul Dolin[2]. *[1]Takeda Development Center Americas, Inc., Deerfield, IL, USA; [2]Takeda Development Centre Europe Ltd., London, UK.*

Background: Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease, often associated with inflammatory bowel disease (IBD). Within CPRD GOLD, there is a specific code for PSC, plus codes for other forms of cholangitis.

Objectives: The study aimed to describe the characteristics of patients with PSC in CPRD GOLD.

Methods: Patients with a Read code for PSC in 1988–2013 but without a secondary sclerosing cholangitis diagnosis any time were eligible. We analyzed patient characteristics before PSC diagnosis among those with at least 1-year data before and after the first diagnosis. Abnormal lab values were defined as >3 times upper limit normal [ULN] for liver enzymes and >1.5 times ULN for total bilirubin.

Results: A total of 371 patients (mean age 54 ± 18 years, men 58.2%) were identified with PSC, of whom 9.7%, 3.2%, and 0.5% also had Read codes for cholangitis, sclerosing cholangitis, and other cholangitis diagnosis, respectively. Of these 371 patients, 222 (59.8%) had at least one liver function test recorded. The number of patients tested and the percentage of patients with abnormal results were as follows: alkaline phosphatase (217, 87.1%), alanine transaminase (178, 55.6%), γ-glutamyl transpeptidase (156, 87.2%), aspartate transaminase (69, 42.0%), and total bilirubin (208, 15.9%). IBD (43.7%, mostly ulcerative colitis 37.2%) was the most common medical history, followed by benign neoplasms (12.9%), cancers (5.9%, solid 5.1%), biliary cirrhosis (2.2%), and liver transplantation (1.4%).

Conclusions: The cohort of patients with a PSC diagnosis in CPRD GOLD had high prevalence of abnormal liver function and IBD co-morbidity. Findings from this study will be used to develop future protocols in CPRD GOLD.

663. Mitigating the Paucity-of-data Problem for Target Population Sizing: Exploring a Model-based Approach for Advanced Gastroenteropancreatic Neuroendocrine Tumors

Alia Yousif,[1] Aurore Bergamasco,[1] Caroline Tremblay,[1,3] Anne-Marie Castilloux,[1] Jérôme Dinet,[2] Gabrielle Nayroles,[2] Sylvie Gabriel,[2] Yola Moride[1,3]. *[1]Yolarx Consultants, Montréal, QC, Canada; [2]Market Access and Pricing, Ipsen Pharma, Paris, France; [3]Faculty of Pharmacy, Université de Montréal, Montréal, Canada.*

Background: Epidemiologic data on neuroendocrine gastroenteropancreatic tumors (GEP-NETs) are scarce in the literature. Thus, sizing the target population to support the real-world value of treatments represents a major challenge.

Objectives: The study aimed to develop a model to estimate the number of patients with specific site and type of GEP-NETs over a 5-year horizon. Study population: Two GEP-NET sub-populations were considered: (i) patients with stable/slow progressing well-differentiated GEP-NETs and unresectable locally advanced/metastatic disease and (ii) patients with stable/slow progressing well-differentiated, non-functioning GEP-NETs and unresectable locally advanced/metastatic disease.

Methods: A literature review was conducted to obtain data on incidence, prevalence, and survival of GEP-NETs in Europe. The following strategy was used: (i) crude prevalence and incidence rates for a broader GEP-NET population identified in the literature; (ii) stratification of estimates according to the above sub-populations derived using proportions of GEP-NETs by site and type using clinical data; and (iii) further stratification of epidemiologic data by clinical experts. A target population growth model mapping the population journey throughout the 5-year period was then developed.

Results: For the first sub-population, the predicted total EU patient number is expected to change from 10 411 to 12 136 in the 5-year span, based on a

prevalence of well-differentiated GEP-NETs of 13.22/100 000 and a proportion of NETs patients with unresectable locally advanced/metastatic disease of 50%. A rate of 50% was then applied to these estimates to derive the number of patients with stable/slow progressing disease. For the second sub-population, the predicted total EU patient number is expected to change from 7288 to 8495 in the 5-year span, since 70% of GEP-NETs are non-functioning.

Conclusions: In the absence of published epidemiologic data on specific sub-populations, the model can be used to estimate trends in target populations under varying labeling hypotheses.

664. Prevalence of Attention Deficit Hyperactivity Disorder in Publically Insured Adults

Yanmin Zhu,[1] Wei Liu,[1] Yan Li,[1] Almut G Winterstein[1]. [1]*Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA.*

Background: No previous literature has estimated adult attention deficit hyperactivity disorder (ADHD) prevalence in Medicaid.

Objectives: The study aimed to estimate the prevalence of diagnosed adult ADHD and its treatment in US Medicaid beneficiaries.

Methods: We used Medicaid Extract Files billing records to establish annual samples of adult Medicaid fee for service beneficiaries from 29 US states in 1999–2010. ADHD was identified based on ≥1 inpatient or 2 outpatient visits with ICD9-CM codes 314.xx. ADHD treatment was determined from pharmacy dispensing records. Eligible patients were required to have 12-month continuous eligibility in the calendar year. We calculated prevalence of ADHD and ADHD drug use in eligible adults and prevalence of ADHD drug use among adults with ADHD. We also calculated percentage of patients with at ≥1 ADHD prescription claims 6 months after ADHD diagnosis and percentage of patients with ADHD diagnosis claims within 6 months before their ADHD drug dispensing in each year.

Results: Prevalence of adult ADHD increased from 2.45 in 1999 to 11.65 per 1000 subjects in 2010. Accordingly, ADHD treatment prevalence increased from 1.95 per 1000 subjects in 1999 to 13.16 per 1000 subjects in 2010. While secular growth was noted across all age groups, prevalence of both diagnosis and treatment was decreasing from the youngest (18–25 years) to older age groups. Males had higher prevalence of both ADHD diagnosis and medication use. The prevalence of ≥1 ADHD prescription claims among adults with ADHD diagnosis increased from 42 in 1999 to 67 per 100 subjects in 2010. We found that the percentage of patients with ≥1 ADHD prescription 6 months after diagnosis was 40% in 1999 and increased to 65% in 2010. Only about 45% in 1999 and 55% in 2010 of all patients with an ADHD prescription had diagnosis claims 6 months before their prescription.

Conclusions: Both prevalence of ADHD diagnosis and its treatment among adults increased from 1999 to 2010. Only half of all ADHD diagnosed adults received treatment, and only half of all patients who received treatment had an ADHD diagnosis. Further investigation should examine whether alternative diagnoses may explain the use of ADHD medication.

665. Association Between Lifestyle and Quality of Life in Healthy Postgraduate Students of India

Shallu Sharma,[1] Deepika Bansal[1]. [1]*Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, India.*

Background: Existing literature has shown the evidence of relation between lifestyle and quality of life (QoL) in various disease conditions. However, there were limited data available about healthy adults of India.

Objectives: The study aimed to examine the relationship between lifestyle and QoL in healthy postgraduate students of India.

Methods: It is an ongoing cross-sectional, questionnaire-based study where healthy postgraduate students were included in the study. After getting the consent, subjects were assessed for demographics, lifestyle using Fantastic lifestyle questionnaire and QoL using SF-36 questionnaire. Fantastic lifestyle questionnaire is interpreted as *excellent* (85–100), *very good* (70–84), *good* (55–69), *fair* (30–54) and *needs improvement* (0–34). Higher total score of SF-36 is interpreted as better quality of life. Summary QoL scores were compared between excellent and very good together with the rest of the groups together using unpaired

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t-test, and differences among the summary scores were assessed using one-way MANOVA.

Results: A total of 100 healthy postgraduate students were included in the study. Participants include 45% females with mean age of 24 (+2.4) years. As per fantastic score, 3, 41, 48 and 8 subjects were found to have excellent, very good, good and fair lifestyle, respectively. None of the subject was in needs of improvement category. Mean QoL score, physical component summary and mental component summary were 51.2 (SD, 3.8), 51.5 (6.5) and 50.8 (6.8), respectively. Although higher total QoL scores were observed in excellent and very good lifestyle together compared with the rest of the groups, it was not statistically significant ($p = 0.22$). However, when difference in summary scores of SF-36 according to lifestyle categories, we found a significant lower mental component summary scores ($p < 0.05$) in excellent and very good lifestyle together compared with rest of the groups. But this difference was not observed in physical component summary score.

Conclusions: Although there was no significant difference in total QoL scores observed according to lifestyle, mental component summary scores were significantly low in subjects with poorer lifestyle.

666. Suboptimal Management of Patients with Non-valvular Atrial Fibrillation: Real-world Clinical Setting

Wallis CY Lau,[1] Esther W Chan,[1] Ian CK Wong[1]. [1]*Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong.*

Background: Anticoagulation treatment is vital for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) but is often underused. As yet, the management of NVAF patients in the real clinical settings is not well described, especially among Asians.

Objectives: The study aimed to identify the proportion of undertreated AF patients and to compare the risk of stroke and mortality among patients using antiplatelet drugs (aspirin/clopidogrel), warfarin, and no therapy.

Methods: Patients newly diagnosed with NVAF during 2010–2012 were identified from the Clinical Data Analysis and Reporting System (CDARS), a population-wide database managed by Hong Kong Hospital Authority. Time in therapeutic range (2–3) was measured using the Rosendaal method, of which ≤40% was defined as poor anticoagulation control. Cox proportional hazards regression was used to assess the risk of stroke and all-cause mortality as a composite outcome in terms of hazard ratio (HR), adjusted for baseline comorbidity.

Results: Among the 27 467 new NVAF patients identified in CDARS, 23 097 (84.1%) were at high risk of stroke (CHA2DS2-VASc ≥2). Only 4809 (21%) of the high-risk patients initiated anticoagulants (warfarin, dabigatran, or rivaroxaban), 14 461 (63%) used antiplatelet drugs only, and 3827 (17%) received no therapy within 1 year after diagnosed with AF. There were 1511 (30.9%) warfarin patients with poor anticoagulation control. Patients who received no therapy were associated with higher risk of stroke and/or all-cause mortality compared with those who received antiplatelet drugs (HR, 1.56; 95%CI, 1.49–1.63), which in turn carried higher risk than those who received warfarin (2.83; 2.61–3.07). Among the warfarin users, patients with poor anticoagulation control were associated with a higher risk of stroke and/or mortality compared with those with better control (2.27; 1.94–2.67).

Conclusions: In the real-world clinical practice, a large proportion of AF patients was undertreated or had suboptimal anticoagulation control. The suboptimal use of antithrombotic therapies was associated with higher risk of stroke and/or all-cause mortality. Measures are needed to optimize the anticoagulation in AF patients.

667. Effect of Antiplatelet Agents Combined with Cilostazol on Cardio–cerebrovascular Events and Bleeding Risk in Acute Coronary Syndrome Patients

Xue-Mei Jin,[1] Ye-Jee Kim,[2] Bo Ram Yang,[1,3] Nam-Kyong Choi,[2] Joongyub Lee,[2] Mi-Sook Kim,[1] Ju-Young Shin,[2] Jong-Mi Seong,[2] Yoosoo Chang,[4] Byung-Joo Park[1]. [1]*Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea;* [2]*Korea Institute of Drug Safety and Risk Management, Seoul, Korea;* [3]*Medical Research Collaborating Center, Seoul National University College of Medicine/Seoul National University Hospital, Seoul, Korea;* [4]*Occupational and Environmental Medicine, Kangbuk Samsung Hospital/Sungkyunkwan University School, Seoul, Korea.*

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Background: The benefit of triple antiplatelet therapy (TAT, combination of cilostazol with aspirin and clopidogrel) for preventing thrombotic events and restenosis in patients after coronary stent implantation in acute coronary syndrome (ACS) patients was reported in several studies. However, the benefit in preventing cardio–cerebrovascular events is still controversial.

Objectives: The aim of the study was to assess the effectiveness between TAT and dual antiplatelet therapy (DAT, aspirin and clopidogrel) on cardio-cerebrovascular events and bleeding risk in ACS patients after coronary stent implantation.

Methods: We performed a retrospective cohort study using Korean Health Insurance Review and Assessment Service database 2009–2013. The patients aged 30–99 years with first diagnosis of ACS (ICD-10: I200, I21) and coronary stent implantation from 1 January 2010 to 31 December 2013 were involved in the study. Patients who received aspirin, clopidogrel and cilostazol were defined as TAT, and those who received aspirin and clopidogrel were defined as DAT. Index date was defined as the first prescription date of DAT or TAT. The Cox proportional hazard model was used to compare the risk of cardio–cerebrovascular (including all-cause mortality, myocardial infarction (MI) and ischemic stroke) and bleeding events in propensity score (PS) matched cohort.

Results: In this study, 30 879 and 9874 patients were identified as DAT and TAT. After PS matching, 9874 patients remained in each group. Compared with those in DAT, the adjusted hazard ratio (aHR) and 95% confidence interval (CI) of cardio–cerebrovascular events and bleeding events in TAT were 2.59 (95%CI: 1.99–3.37) and 1.00 (95%CI: 0.77–1.22), respectively. And the aHRs for all-cause mortality, MI and ischemic stroke were 1.91 (95%CI: 0.06–58.89), 4.32 (95%CI: 2.79–6.69) and 2.45 (95%CI: 1.60–3.75) in TAT compared with DAT.

Conclusions: Cilostazol-based TAT was associated with higher risk of cardio–cerebrovascular events compared with DAT, significantly. And higher risk of MI and ischemic stroke was also found in TAT. There is a need for caution when choosing TAT.

668. Persistence to Oral Anticoagulant Therapy in Japanese Atrial Fibrillation Patients

Hiraku Kumamaru,[1] Chisa Matsumoto,[2] Soko Setoguchi[3]. *[1]Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA; [2]Division of Cardiology, Tokyo Medical University, Tokyo, Japan; [3]Duke Clinical Research Institute, Durham, NC, USA.*

Background: Little is known regarding how persistent atrial fibrillation (AF) patients are to oral anticoagulant therapy in Japan where frequent (≥monthly) visits to their primary care physicians are common.

Objectives: The study aimed to examine and compare the persistence to dabigatran and warfarin among AF patients initiating oral anticoagulant therapy in Japan.

Methods: We constructed a cohort of patients aged 18 years or older initiating warfarin or dabigatran between March 2011, when dabigatran entered the market, and May 2013 using Japan Medical Data Center claims database. Patients without prior diagnosis of AF were excluded. We followed the patients until discontinuation (>14-day coverage gap). Patients were censored at dispensation of another type of anti-coagulant, dis-enrollment from the plan, end of study period (August 2013), or at 365 days from the date of initiation. Time to discontinuation was compared between warfarin and dabigatran initiators using Cox proportional hazards model adjusting for demographic variables.

Results: We identified 548 dabigatran and 708 warfarin initiators, respectively. Dabigatran initiators were slightly younger. During the median follow-up of 195 days for dabigatran and 235 days for warfarin, 154 (28.2%) and 152 (21.5%) of the patients discontinued their medication. Switching to another anti-coagulant occurred in 42 (7.7%) vs. 51 (7.2%) of the users, respectively. After adjusting for age and gender, dabigatran initiators had close to 50% higher hazard of discontinuation compared with warfarin initiators (adjusted hazard ratio = 1.48 (95% confidence interval: 1.18–1.85).

Conclusions: Persistence to anticoagulant therapy for AF patients in Japan was low, especially for dabigatran users, similarly to what has been reported in other countries. Studies to identify and intervene on the individuals with higher risk of non-persistence were necessary.

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669. Persistence of Dabigatran Versus Warfarin Therapy in Patients with Non-valvular Atrial Fibrillation in the Real-world Clinical Practice

Wallis CY Lau,[1] Esther W Chan,[1] Ian CK Wong[1]. [1]*Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong.*

Background: Dabigatran, a direct thrombin inhibitor, is the first approved new oral anticoagulant claiming as a better alternative to warfarin without the need of monitoring. While treatment persistence is crucial for the optimal use of anticoagulation therapy, data from the existing literature comparing the persistence rates between dabigatran and warfarin are limited.

Objectives: The study aimed to evaluate and compare the persistence of dabigatran and warfarin therapy in patients with non-valvular atrial fibrillation (NVAF).

Methods: Patients newly diagnosed with NVAF who received dagbiatran or warfarin during 2010–2013 were identified from the Clinical Data Analysis and Reporting System (CDARS), a population-wide database managed by Hong Kong Hospital Authority, which serves over seven million people in Hong Kong. Discontinuation of therapy was defined as having >60 days of interval between prescription refills. Propensity score matching was applied to control for any heterogeneity between treatment groups. Kaplan–Meier estimates of survival was used to assess the persistence rate at the end of 3-month, 6-month, and 1-year period. Sensitivity analyses were conducted using a 30-day permissible medication gap.

Results: In total, 6834 and 2106 patients with NVAF receiving dabigatran and warfarin were identified in CDARS. Of these, 2106 propensity-score-matched pairs were included in the analysis. The mean time to discontinuation was 149 days (standard deviation [SD] = 180) and 152 days (SD = 189) in dabigatran and warfarin users, respectively. Using a 60-day permissible medication gap, the persistence rates were lower for dabigatran compared with warfarin for 3-month, 6-month, and 1-year period (72.8% vs. 81.9%, log-rank test $p < 0.001$; 56.8 vs. 76.7%, $p < 0.0001$; 49.1% vs. 70.8%, $p < 0.0001$). Sensitivity analysis using 30-day permissible medication gap yielded similar results.

Conclusions: In this study, the persistence rate of dabigatran users was lower than that of warfarin users. Further research is needed to investigate the reasons for discontinuation and improve drug compliance.

670. Increasing Atomoxetine and Decreasing Methylphenidate Use for Pediatric Patients with Attention Deficit Hyperactivity Disorder (ADHD) in Korea

Ju-Young Shin,[1] Sun Mi Shin,[1] Shin Haeng Lee,[1] Han Na Shin[1]. [1]*DUR Information, Korea Institute of Drug Safety and Risk Management, Seoul, Korea.*

Background: Increasing prevalence of attention deficit hyperactivity disorder (ADHD) and methylphenidate use worldwide were reported. However, the changing patterns of drug use have not been investigated after the introduction of a newer drug, atomoxetine, in 2006.

Objectives: The aim of this study was to investigate the prevalence of methylphenidate and atomoxetine use in Korean pediatric patients with ADHD.

Methods: We used Korea National Health Insurance Corporation (NHIC) claims database between 1 January 2007 and 31 December 2011. Study subjects consisted of pediatrics younger than 18 years old who were diagnosed with ADHD (ICD-10, F90) with prescriptions of methylphenidate or atomoxetine. Monthly proportion was calculated according to the prescribed ADHD medication. All analyses were performed for boys and girls. Cochrane–Armitage test was performed to calculate the p for its trend.

Results: The total number of 75 377 ADHD patients/year was identified from 2007 to 2011 (boys – 79.7%, girls – 20.3%; p-value < 0.05). Approximately three-quarters of the ADHD patients were prescribed methylphenidate or atomoxetine (total – 72.2%, boys – 73.0%, girls – 69.2%; p-value < 0.05). We found an increasing prevalence of ADHD medication use among pediatric patients with ADHD (boys – 74, 83% in 2007 to 78.38% in 2011, p for trend <0.05; girls – 70.31% in 2007 to 73.50% in 2011, p for trend <0.05). The increasing pattern was observed in atomoxetine use since September 2009 (boys – 6.09% in 2009 to 13.74% in 2011, p for trend <0.05; girls – 4.50% in 2009 to 10.67% in 2011, p for trend <0.05), whereas a decreasing pattern was observed in methylphenidate use (boys – 74.83% in 2007 to 71.09% in 2011, p for trend <0.05; girls – 70.31% in 2007 to 67.47% in 2011, p for trend <0.05).

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Conclusions: The pattern of increased atomoxetine use was observed since September 2009, whereas methylphenidate use decreased in both boys and girls with ADHD. More research would be needed to show how the change in epidemiology of ADHD medication use affected the safety and efficacy of ADHD treatments.

671. Validity of a Claims-based Stroke Severity Index for Hospitalized Acute Ischemic Stroke Patients

Cheng-Yang Hsieh,[1,2] Sheng-Feng Sung,[3] Huey-Juan Lin,[4] Yu-Wei Chen,[5] Chih-Hung Chen,[6] Yea-Huei Kao Yang,[2] Ya-Han Hu[7]. *[1]Department of Neurology, Tainan Sin Lau Hospital, Tainan, Taiwan; [2]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [3]Division of Neurology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan; [4]Department of Neurology, Chi Mei Medical Center, Tainan, Taiwan; [5]Department of Neurology, Landseed Hospital, Taoyuan, Taiwan; [6]Department of Neurology, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [7]Department of Information Management, Institute of Healthcare Information Management, National Chung Cheng University, Chiayi, Taiwan.*

Background: It has been difficult to adjust stroke severity in studies based on claims data because clinical stroke scales are unavailable.

Objectives: We aimed to assess the validity of a novel claims-based stroke severity index (SSI) and determined whether it improved case-mix adjustment.

Methods: We analyzed 4777 adult patients with AIS from two hospital-based stroke registries linked with a nationwide claims database (National Health Insurance Research Database). We calculated the SSI for each patient by using billing codes from the claims files. Actual stroke severity by the National Institutes of Health Stroke Scale (NIHSS) and functional outcomes by the modified Rankin Scale (mRS) were retrieved from the stroke registries.

Results: The SSI correlated with the NIHSS at admission ($r = 0.708$; 95% confidence interval, 0.694–0.722) and correlated with the mRS at 3 months (0.598; 0.577–0.618) at 6 months (0.578; 0.556–0.600) and at 1 year (0.557; 0.528–0.583). Mortality models (age, gender and Charlson's comorbidity index) with the SSI had better discrimination than those without (*c* statistic, 0.859 versus 0.739, $p < 0.001$ for 3-month mortality; 0.834 versus 0.741, $p < 0.001$ for 6-month mortality; 0.814 versus 0.732, $p < 0.001$ for 1-year mortality). The *c* statistics between models with the SSI and models with the NIHSS did not differ significantly.

Conclusions: The SSI improved case-mix adjustment of mortality models and can act as a valid proxy for stroke severity for future study of AIS patients based on claims data.

672. Myocardial Infarction Associated with Current Use of Helicobacter Pylori Eradication Regimen Containing Clarithromycin: Self-controlled Case Series

Angel YS Wong,[1] Adrian Root,[2] Ian Douglas,[2] Celine Chui,[1] Esther W Chan,[1] Yonas Ghebremichael-Weldeselassie,[3] Liam Smeeth,[2] Ian CK Wong[1]. *[1]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong; [2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; [3]Department of Mathematics and Statistics, The Open University, Milton Keynes, UK.*

Background: Clarithromycin is a commonly prescribed macrolide and is also used as part of treatment regimen to eradicate *Helicobacter pylori* infection in Hong Kong (HK). Recent observational studies reported its association with an increased risk of long-term cardiovascular events.

Objectives: The study aimed to investigate the association between the use of clarithromycin for *H. pylori* eradication and myocardial infarction (MI).

Methods: A self-controlled case series (SCCS) study was conducted using the Clinical Data Analysis and Reporting System (CDARS) database in HK. The exposure was *H. Pylori* eradication triple therapy containing clarithromycin prescribed in the outpatient setting. Study subjects had both the drug exposure and an incident MI as principal diagnosis in the accident and emergency or inpatient setting from 1 January 2003 to 31 December 2012. Several risk windows were defined: 14-day pre-exposure, current use (day 1–14 since prescription start date), recent

use (day 15–30), and past use (day 31–90, day 91–365, day 366–730, day 731–1095). Incidence rate ratios (IRR) were estimated using Poisson regression, comparing the rates of event between risk windows with the rate during baseline periods. A non-parametric SCCS method where no risk windows are pre-specified was also applied. As MI might increase mortality in the short term, which may affect the assumption of event independence in standard SCCS, sensitivity analysis was also performed to remove patients who died within 3 months after first recorded MI.

Results: We identified 740 patients who had both outpatient triple therapy for *H. pylori* and incident MI. An IRR of 3.38 (95% confidence interval [CI] 1.89 to 6.04) was found in current use. No increased risk of MI was found during all other risk windows before or after the exposure. IRR functions estimated from the non-parametric SCCS method showed similar results. Similarly, increased risk of MI was only found during the current use in the sensitivity analysis (IRR 3.07; 95%CI 1.58 to 5.97).

Conclusions: This study found an increased short-term risk of MI during current use of triple therapy among the HK population.

673. Withdrawn by author

674. The Gender Differences in the Short-term and Long-term Treatment Outcomes in Taiwan Rheumatiod Arthritis Patients

Tzu-Chieh Lin,[1,2] Yea-Huei Kao Yang,[1,2] Swu-Jane Lin[3]. *[1]Insititute of Clinical Pharmacy and Pharmaceutical Science, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [3]Department of Pharmacy Administration, University of Illinois at Chicago, Chicago, IL, USA.*

Background: There were reports suggested that female RA patients may have higher systematic inflammatory factors than male; we therefore hypothesized that there might be gender differences in disease progression and CVD risk in RA patients.

Objectives: The study aimed to compare the relative risk of starting biologic agents (short-term outcomes) and composite CVD endpoints (long-term outcomes) after receiving methotrexate-based regimen between female and male RA patients.

Methods: A retrospective cohort study was conducted using the National Health Insurance Research Database in Taiwan, including RA patients who had catastrophic illness status and ever received methotrexate (MTX)-based regimens from 2005 to 2009. The first-date patients who received MTX was defined as the index date, and every patient was followed from the index date till non-persistent, event occurred; death; or the end of the study (31 December 2010). The persistency of treatment during a follow-up was confirmed by allowing a 90-day grace period. Multiple Cox regression models were constructed to compare the relative risk in starting biologic agents, and female patients were the control group. When comparing the relative risk in composite CVD endpoints (MI, stroke, or coronary re-vascularization), ever use of biologic agents was further treated as a time-dependent variable in the Cox model.

Results: From 2005 to 2009, there were 12 882 RA patients who entered our cohort, and 2829 (22%) patients were male. As compared with male, female patients were younger (52.1 ± 13.6 vs. 55.3 ± 13.7 years old), more prevalent in osteoporosis, use of hydroxyquoloqine, and lower socioeconomic status. Results of multiple Cox regression showed there was no gender difference in the risk of starting biologic agents (adjusted HR, 0.97; 95%CI, 0.87–1.09); however, male patients may have two-fold higher risk for composite CV endpoints (adjusted HR, 1.92; 95%CI, 1.44–2.56). Results were consistent in sensitivity analyses.

Conclusions: We found that there were gender differences in the risk of CVD in Taiwan RA patients under MTX-based therapy. Aggressive screening for CVD risk factors and primary or secondary prevention actions are crucial in male RA patients.

675. Comparison of High-potency Statin Monotherapy and Statin Plus Ezetimibe Combination Therapy for Reducing Cardiocerebrovascular Disease Risk

Bo Ram Yang,[1,2] Joongyub Lee,[2] Nam-Kyong Choi,[2] Ju-Young Shin,[3] Yoosoo Chang,[4] Hong-Ji Song,[5] KyungEun Youn,[6] Xue-Mei Jin,[1] Mi-Sook Kim,[1] Ye-Jee Kim,[3] Jong-Mi Seong,[3] Byung-Joo Park[1].

[1]Seoul National University College of Medicine, Seoul, Korea; [2]Medical Research Collaborating Center, Seoul National University College of Medicine/ Seoul National University Hospital, Seoul, Korea; [3]Korea Institute of Drug Safety and Risk Management, Seoul, Korea; [4]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea; [5]Hallym University College of Medicine, Chuncheon; [6]Korea Food and Drug Administration, Cheongwongun, Korea.

Background: Hypercholesterolemia is a risk factor of cardiovascular disease, and statin is the first-line therapy of treatment. As high-dosage statin therapy was known to be associated with muscular adverse events and diabetes, statin and ezetimibe combination therapy was introduced for effective lipid lowering therapy. It is important to evaluate the risk of clinical outcome related to statin and ezetimibe combination therapy such as cardio-cerebrovascular disease (CVD) compared with statin monotherapy.

Objectives: The aim of the study was to compare the risk of incident CVD in patients who began statin–ezetimibe combination therapy versus those who began high-potency statin monotherapy.

Methods: We conducted a retrospective cohort study using Korean Health Insurance Review and Assessment Service database between 2008 and 2012. Patients aged 20 to 99 years who were prescribed statin or statin and ezetimibe in 2009 were included. We excluded the patients who began therapy with low-potency statin, received either study drug prescription in 2008, or had previous CVD event. Incident CVD was identified as admission due to acute myocardial infarction (ICD-10: I21), ischemic stroke (I63), or procedure including coronary artery bypass graft, percutaneous coronary intervention, thrombolytic treatment, or percutaneous transluminal angioplasty. We matched patients with statin–ezetimibe combination therapy to statin monotherapy using a propensity score (PS). The adjusted hazard ratios (aHRs) were estimated by using Cox proportional hazards model for controlling confounders.

Results: We identified 17 040 patients with statin–ezetimibe combination therapy and 196 769 patients with statin monotherapy. After 1:1 matching by PS, 17 040 patients were remained in each group. Compared with that of statin monotherapy, the adjusted HR (aHR) of statin–ezetimibe combination therapy for incident CVD was 0.65 (95% CI: 0.47–0.91) in PS-matched cohort. The aHR was 0.29 (95%CI: 0.12–0.72) for acute myocardial infarction and 0.62 (95%CI: 0.36–1.05) for ischemic stroke.

Conclusions: Statin–ezetimibe can significantly reduce the risk of incident CVD compared with statin monotherapy.

676. Risk of Peptic Ulcer Among Antidepressants Users with or Without Concurrent Use of Non-steroidal Anti-inflammatory Drugs: Nationwide Propensity Score Matched Study

Ju-Young Shin,[1] Mi-Ju Park,[1] Shin Haeng Lee,[1] So-Hyun Choi,[1] Byung-Joo Park[2]. *[1]DUR Information, Korea Institute of Drug Safety and Risk Management, Seoul, Korea; [2]Department of Preventive Medicine, Seoul National University, College of Medicine, Seoul, Korea.*

Background: It is generally believed that antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are associated with a higher risk of peptic ulcer, and non-steroidal anti-inflammatory drugs (NSAIDs) potentiate this risk. However, a recent cohort study reported contrary results, and no epidemiology study has been performed on tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SNRIs).

Objectives: The study aimed to evaluate the risk of peptic ulcer among patients, who were treated with antidepressants and NSAIDs, compared with the risk among those treated with antidepressants alone and to compare the risk according to the classes of antidepressants

Methods: We conducted a retrospective cohort study involving 1 127 622 patients who began receiving a new antidepressant medication between 2009 and 2012 using Korean Health Insurance Review and Assessment Service (HIRA) database. Combined use of NSAID was defined as the prescription of at least one NSAID within 7 days of antidepressants use. Propensity-based matching was performed in a 1:1 ratio using greedy matching macro. Time to first hospitalization with peptic ulcer (ICD-10: K25-28) was identified. Cox proportional-hazards models were used to compare the risk of peptic ulcer among patients who were treated with antidepressants and NSAIDs compared with those with antidepressants alone.

Results: The propensity-matched cohort used in the analysis included a total of 768 850 persons. The risk of peptic ulcer increased with the combined use of antidepressants and NSAIDs, as compared with the use of antidepressants alone (hazard ratio [HR], 1.13; 95% confidence interval [CI], 1.09 to 1.17). We observed higher increased risks in TCAs (HR, 1.24; 95% CI, 1.17 to 1.32), SNRIs (HR, 1.26, 95%CI, 1.00 to 1.58), and SSRIs (HR, 1.25; 95%CI, 1.15 to 1.34).

Conclusions: The combination use of TCAs, especially SNRIs and SSRIs, and NSAIDs is associated with a risk of peptic ulcer. Caution will be needed when prescribing both drugs together.

677. Prescribing Patterns of Antidepressants for the Elderly Depressive Patients in Korea

Kyoung-eun Kwon,[1] Ju-Young Shin,[2] Ye-Jee Kim,[2] Nam-Kyong Choi,[3] Joongyub Lee,[3] Byung-Joo Park[1]. *[1]Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea; [2]Korea Institute of Drug Safety and Risk Management, Seoul, Korea; [3]Medical Research Collaborating Center, Seoul National University Hospital/Seoul National University College of Medicine, Seoul, Korea.*

Background: Several studies have revealed that the prevalence of depressive disorders in the elderly population ranges from 10 to 20%, and it is a debilitating psychiatric disorder which is considered as an important public health concern. However, there is a lack of information on the prescribing patterns of antidepressants (ADs) in Korean elderly population.

Objectives: The aim of this study was to investigate the nationwide trend of using ADs in Korean elderly depressive patients.

Methods: Our study was conducted using Korea Health Insurance Review and Assessment Service-Adult Patient Sample (HIRA-APS) database. We identified patients who were diagnosed as depression (ICD-10: F32, F33) without psychotic disorders and prescribed at least one AD in 2011. We conducted descriptive analysis for patient characteristics and the use of ADs. Chi-square test was used to comparing prescription patterns of ADs between the types of medical institutions, regions and doctor's specialties.

Results: During the study period, the number of claims for AD prescription was 228 379 for 27 966 elderly depressive patients; 65% were female, and the mean age was 73.3 (±5.81) years. Proportion of male patients treated with ADs was higher in age group of 65–69 years (33.9%), while 70–74-year age group was the most frequently prescribed in female patients (30.9%) ($p < 0.01$). Monotherapy was 86.1% of all prescriptions. The commonest prescribed drug was TCAs (55.3%), followed by atypical ADs (23.7%). Among the combination therapy regimens, a SSRI and an atypical AD were combined most frequently (29.5%), and co-prescription of a TCA-a SSRI had occupied 23.8%. There were differences in the number of ADs per prescription, kinds of drugs prescribed and combination types depending on the regional area, type of medical institution and doctor's specialty (all $p < 0.01$).

Conclusions: More than half of the study population was prescribed TCAs, although TCAs are not recommended for elderly patients. And large differences among regions, medical institutions and doctor's specialties were observed. More research efforts for developing guidelines to prevent inappropriate prescribing ADs in Korean elderly depressive patients are needed.

678. Geographic Variation and Type of Medical Service in the Prescribing Pattern of Zolpidem Use in Korea

Hyo-Ju Park, Ju-Young Shin, Han-Na Shin. *Office of Drug Utilization Review (DUR), Korea Institute of Drug Safety and Risk Management (KIDS), Seoul, Korea.*

Background: Zolpidem, non-benzodiazepine hypnotic, is widely used to treat insomnia. However, some case reports about psychoactive disorder, drug abuse and withdrawal response have been reported.

Objectives: The study aimed to analyze the prescription pattern of zolpidem to know how many healthcare providers follow the recommended dosage and treatment duration.

Methods: The analyzed data are the National Patient Sample data of 2011 retrieved from the Health Insurance Review and Assessment Service (HIRA), which contains information on claims of Korean population. The patient's characteristics prescribed zolpidem were analyzed in terms of age, gender and prescribed form. The maximum daily dose of zolpidem is 10 mg for immediate release (IR) form and 12.5 mg for controlled

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release (CR) form, and the maximum single treatment duration of zolpidem is 28 days for IR form in the Korean monograph of zolpidem. According to the monograph, the number, proportion, physician specialty and regional variation of prescription exceeding the maximum daily dose and single treatment duration were analyzed.

Results: The prescriptions exceeding the recommended dosage and duration were confirmed. The prescribed dose of CR form was exceeded in 386 of 8957 prescriptions (4.31%), and that of IR form was exceeded in 3123 of 90 938 prescriptions (3.44%). The prescribed duration of IR form was exceeded in 15 956 of 90 938 prescriptions (17.5%). There were various physician specialties prescribing zolpidem over the recommended daily dose and single treatment duration besides neuropsychiatry. The regional variation in prescription over the maximum daily dose and treatment duration were observed (p-value < 0.05).

Conclusions: Zolpidem is relatively safe hypnotics but is able to cause various adverse events especially in paediatrics or eldery patients if administered for excessively high dose and long duration. Therefore, zolpidem should be prescribed cautiously, and both the health providers and the patients need to recognize the benefit and risk of zolpidem for insomnia.

679. A Survey on Self-medication with Antibiotics and over the Counter Drugs Among Undergraduate Medical Students in Yogyakarta, Indonesia

Sharonjit Sandhu[1]. [1]*Medicine, Gadjah Mada University, Yogyakarta, Jave Tengah, Indonesia.*

Background: Studies have shown the prevalence of self-medication among medical students worldwide. However, there is lacking evidence on this in Yogyakarta, Indonesia.

Objectives: The aim of the study was to determine the extent of self-medication with antibiotics and OTC drugs among undergraduate medical students.

Methods: This study employed a cross-sectional design implemented in the form of a pre-validated, self-administered questionnaire. The study population consisted of 96 undergraduate medical students selected using a systematic random sampling approach and currently enrolled in first to fourth year in the Faculty of Medicine at Gadjah Mada University. Data collected was analyzed using Chi-square test and and Fisher's exact test. A p-value of <0.05 was considered significant for this study.

Results: A 100% response rate was received with all questionnaires completely filled out. Out of the 96 students, 49% were found to have engaged in self-medication within the past 1 year. Self-medication with both antibiotics and OTC drugs was found in 47% of all students, while 2% of students self-medicated with only OTC drugs. Families played a major role in contributing information to these students on the drugs that they self-medicated with (64%). Pharmacies were the most common source of obtaining these drugs (70%). The most common condition treated with self-medication was headache (79%). The most common antibiotic and OTC drug used for self-medication were amoxicillin (62%) and paracetamol (94%), respectively. The main reason for self-medicating was convenience (62%). From the students who self-medicated with antibiotics, 40% do not intend to stop this practice in future. Significant associations were found between having health insurance and the practice of self-medication ($p = 0.034$) as well as increased knowledge on antibiotic function and year of study ($p < 0.05$).

Conclusions: Self-medication is prevalent among medical undergraduate students here in Yogyakarta, Indonesia. Actions should be taken to educate all students on the hazards of irrational drug use. There is a dire need for stringent monitoring of drug distribution here in Yogyakarta, Indonesia.

680. Survey on Self-medication of Vitamin and Supplement Among Medical Undergraduate Students in Yogyakarta, Indonesia

Yana Suryani.[1] [1]*Gadjah Mada University, Yogyakarta, Indonesia.*

Background: The popularity of dietary supplement and its self-medication has been increasing over the years. Unlike developed countries, not many studies have been done to investigate the practice of self-medication of dietary supplement in Indonesia.

Objectives: This study is conducted to investigate the practice of self-medication of vitamin and supplement among medical students of Universitas Gadjah Mada (UGM) in Yogyakarta, Indonesia, and their knowledge, perception and attitude towards it.

Methods: A survey was conducted in the Faculty of Medicine, UGM. Ninety-six first to fourth year medical students were selected via stratified random sampling and required to answer a 58-question self-administered questionnaire each. Questions asked in the questionnaire include those relating to demographic characteristics and lifestyle of students and their self-medication practice, attitude, perception and knowledge on vitamin and supplement. Data collected were analysed using Chi-square or Fisher's exact test with significance cut-off point of $p < 0.05$.

Results: It is found that 60% of the students practise self-medication of vitamin and supplement. Commonly consumed supplements are vitamin C (69%), multivitamin (29%) and calcium (22%). Main reasons for supplement intake were to maintain general health (91%) and parents' order (21%) and to improve physical appearance (10%). Family (78%), internet (24%), friends (16%) and television (16%) are the common sources of information on supplement, while popular sources to obtain supplement are pharmacy (57%), family (19%), supermarket (16%) and online shopping (9%). Most students (71%) believe that the supplement taken is beneficial, and nausea, the only reported adverse effect, was only faced by 3% of the students. Demographic characteristics and knowledge were shown to have no significant association with the practice of self-medication.

Conclusions: Majority of the medical students self-medicate occasionally with vitamin and supplement and find them helpful. However, the knowledge of the students on vitamin and dietary supplement are found to be lacking and warrants for further intervention.

681. Myocardial Infarction and Cardiac Death Associated with Current Use of Clarithromycin: Cohort Study

Angel YS Wong,[1] Adrian Root,[2] Ian Douglas,[2] Celine Chui,[1] Esther W Chan,[1] Liam Smeeth,[2] Ian CK Wong[1]. *[1]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong; [2]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK.*

Background: Clarithromycin is a commonly used macrolide in Hong Kong (HK). In recent studies, it was found to be associated with an increased risk of cardiovascular events or cardiac mortality.

Objectives: The study aimed to compare the risk of myocardial infarction (MI) and cardiac mortality among clarithromycin users with amoxicillin/Co-amoxiclav (AMX) users.

Methods: A population-based cohort study was conducted using the Clinical Data Analysis and Reporting System (CDARS) in HK. All patients aged ≥18 years and prescribed either oral clarithromycin or AMX during 2005–2009 were identified and then followed for up to 3 years with the observation period of 1 January 2005 to 31 December 2012. Each clarithromycin user was matched to up to two AMX users based on age, sex and calendar year at exposure. Patients who were prescribed clarithromycin up to 4 years before the date of first antibiotic prescription during the observation period were excluded in both groups. The primary and secondary outcomes were the first recorded MI and cardiac death during the observation period, respectively. Follow-up periods were classified as current use (day 1–14 since prescription start date), recent use (day 15–30) and past use (day 31–90, day 91–365, day 366–730, day 731–1095). Poisson regression was used to estimate the rate ratios (RR) with initial adjustment for age, sex and history of MI. Propensity score (PS) adjustment with trimming was also used to control for confounding.

Results: We matched 108 988 clarithromycin users to 217 793 AMX users. For current use of clarithromycin versus AMX, the RR for MI with initial adjustment was 2.65 (95% confidence interval 2.25 to 3.12) and the PS adjusted RR was 3.29 (2.74 to 3.94). The initial adjusted RR for current use of clarithromycin versus AMX for cardiac mortality was 1.98 (1.66 to 2.36) and 1.71 (1.39 to 2.10) with PS adjustment. No increased risk of MI or cardiac death was observed in recent or past use of clarithromycin.

Conclusions: Current exposure to clarithromycin demonstrated an association with MI and cardiac mortality; however, no long-term effect was observed.

682. Association Between an Excess Risk of Anaphylaxis and Concomitant Use of Benzylpenicillin and Herba Houttuyniae Injection, Retrospective Analysis of a Spontaneous Reporting System

Haona Li,[1] Jianxiong Deng,[2] Yiexiang Zhang,[2] He Sun[1]. *[1]Tianjin University, Tianjin, China; [2] Provincial ADR Centre of Guangdong, Guangzhou, China.*

Background: Interaction between drugs may yield excess risk of adverse drug reactions. For many widely used modern medicines, like benzylpenicillin, the possible interactions with modern medicines have been well established. But little is known about the effects of interactions between modern medicines and traditional Chinese medicines.

Objectives: The aim of the study was to investigate the excess risk of anaphylaxis resulting from a possible interaction between benzylpenicillin and herba houttuyniae injection (a widely used traditional Chinese medicine).

Methods: Data used in the study are from China Provincial ADR Centre of Guangdong from 2004 to 2013. We studied suspected ADR reports using a case/non-case design. The cases were defined as the reactions coded by WHO preferred terms of anaphylactic shock or anaphylactoid reaction. Exposure categories were the use of benzylpenicillin or herba houttuyniae versus the use of neither of both drugs. The influence of the combined use of both drugs was examined using reporting odds ratios (RORs) and the shrinkage measure method (Ω).

Results: The crude RORs for anaphylaxis in patients who used only benzylpenicillin or herba houttuyniae injection and those who used the two drugs concomitantly (compared with the use of neither of both drugs) were 2.45 (95%CI: 2.28–2.63), 11.08 (95%CI: 9.17–13.38) and 23.67 (95%CI: 8.21–68.23), respectively. After being adjusted for gender, age and year of reporting, the adjusted RORs changed to 2.19 (2.04–2.35), 2.97 (2.44–3.61) and 5.78 (1.99–16.75), respectively. The measured Ω, Ω_0, Ω_025 and Ω_975 was 1.95, 2.24, 0.78 and 2.78, respectively.

Conclusions: The results of RORs and Ω_025 suggest that the concomitant use of benzylpenicillin and herba houttuyniae injection may yield an excess risk of anaphylaxis. Individual case safety reports can be used in detecting possible interactions between modern medicines and traditional Chinese medicines.

683. The Association Between Oral Fluoroquinolones and Seizures: A Hong Kong and United Kingdom Population-based Self-controlled Case Series Study

Celine SL Chui,[1] Esther W Chan,[1] Angel YS Wong,[1] Adrian Root,[2] Ian J Douglas,[2] Ian CK Wong[1]. *[1]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China [2]Department of Non-Communicable Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK.*

Background: Case reports have reported potential association between the use of oral fluoroquinolones (FQ) and the subsequent development of seizure. However, evidence from formal studies is limited.

Objectives: The aim of the study was to determine the incident rate ratio (IRR) of incident seizure among patients prescribed oral FQ in Hong Kong (HK) and the United Kingdom (UK).

Methods: This study was conducted using the Clinical Data Analysis and Reporting System (CDARS, HK) and Clinical Practice Research Datalink (CPRD, UK). Self-controlled case series design was used. Patients prescribed ≥1 oral FQ prescription and who had incident seizure diagnosis from 2001 to 2013 were identified. Those with a history of seizure, febrile or traumatic convulsion were excluded. The IRRs were estimated with Poisson regression in risk windows pre 8–14 days, pre 7 days, FQ prescription, post 7 days and post 8–28 days compared to baseline period. Sensitivity analysis comparing the first 7 days of FQ prescription with pre 7 days as baseline was conducted to determine whether the increased risk of seizure was associated with FQ or the infection. The IRRs of the two settings were meta-analysed to obtain the summary effect.

Results: A total of 2208 and 4177 cases from CDARS and CPRD were included in the analysis, respectively. IRRs pre-risk period of both databases were significantly increased. IRRs of the FQ prescription period were 1.38 (95% confidence interval [CI] 0.88–2.17) and 1.66 (95%CI 1.23–2.24) in CDARS and CPRD, respectively. The IRRs in the post-risk periods decreased and were close to 1.00 for both databases. Sensitivity analysis estimated IRR of 0.91 (95%CI 0.43–1.95) in CDARS and 1.24 (95%CI 0.74–2.08) in CPRD. The meta-analysis of the FQ prescription periods resulted in an IRR of 1.62 (95%CI 1.27–2.08) with $I^2 = 0\%$.

Conclusions: This study showed a significant association between oral FQ and incident seizure in the meta-

analysis. However, such association was also observed in the pre-risk periods. We suspect that the infection that occurred prior to the prescription of oral FQ may have contributed to the development of seizure rather than the drug itself.

684. Cardiotoxicity of Adjuvant Trastuzumab in Taiwan Breast Cancer Patients: A Population-based Study

Hsu-Chih Chien,[1] Yea-Huei Kao Yang,[1,2] Jane PF Bai.[3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [3]Office of Clinical Pharmacology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA.*

Background: Few data are available regarding the risk for trastuzumab (HER) cardiotoxicity in Asian breast cancer (BC) patients.

Objectives: The aim of the study was to quantify the risk for HER treatment-related cardiotoxicity in Taiwanese BC patients.

Methods: We identified female BC patients who received medical interventions from National Health Insurance Research Database of Taiwan, between 2002 and 2009. BC patients with congestive heart failure and cancer history prior to BC diagnosis were excluded. The incidence of treatment-related CHF/CM was estimated. Descriptive statistics and Cox proportional hazard model were employed for data analysis. The use of HER was a unidirectional time-dependent variable, while chemotherapy (CT) and radiation therapy cumulative cycles were time-dependent covariates in our Cox model. We applied PS matching, weighting, and stratification to assess HER-related cardiotoxicity. Confounding covariates in our PS model included patient-level demographic data, comorbidity index, cardiovascular specific comorbidities and related medication, and cancer-related treatments and checkups. We also performed sensitivity analysis.

Results: Among the 31 413 newly diagnosed BC patients during 2002 to 2009, 21 230 were treated with CT, while others were not. Of all CT receivers, 2070 women were prescribed with HER; 640 patients received HER-containing regimens in their initial CT treatments. The crude incidence of CHF/CM in HER users and non-HER users was 4.93% and 2.86% ($p < 0.0001$), respectively. Compared with non-HER users, HER users had a higher risk for CHF/CM after adjustment for PS and other covariates in a multiple regression model (aHR = 2.40, 95%CI, 1.54–3.74). We also estimated the risk for HER cardiotoxicity by PS weighting (IPTW population: HR = 2.37, 95%CI, 1.96–2.86; SMRW estimation: HR = 2.17, 95%CI, 0.96–4.87) and matching (greedy match, with five controls per case: HR = 4.40, 95%CI, 2.38–8.13; optimal match: HR = NA, 95%CI, NA). We did not acquire appreciable differences in sensitivity analyses. We are expecting results from optimal match and competing risk regression model.

Conclusions: Trastuzumab was associated with increased CHF/CM risk in Taiwan BC population.

685. Withdrawn by author

686. An Indian Study on Assessment of the Suitability of Pharmacotherapy in Elderly Patients and Its Enhancement

Mandavi Kashyap, Mangu Rohit, Vinay Kapur, Sanjay D'Cruz, Atul Sachdev, Pramil Tiwari. *[1]AIMST University, Semeling, Malaysia; [2]NIPER, Mohali, India; [3]GMCH, Chandigarh, Chandigarh, India;*

Background: Elderly patients present with multiple diseases and are prescribed multiple medicines, which may raise the chances of inappropriate prescription and drug-related problems.

Objectives: The study aimed to determine the prevalence of inappropriate drug use and predictors of inappropriate prescribing pattern in Indian elderly inpatients.

Methods: Study Design: 1-year prospective interventional

Setting: Inpatient wards of the General Medicine department of a public hospital.

Participants: Inpatient 60 years or older ($n = 643$).

Intervention: Provided regular feedback and documented changes in therapy made by physicians.

Measurements: Modified updated Beers Criteria 2012 used to identify inappropriate medication.

Results: The mean age of the patients was 68.44 ± 0.30 years. Each patient had 2.07 ± 0.04 diagnoses and was prescribed 7.57 ± 0.12 medications. According to the Beers criteria, inappropriate drug prescribing was found in 42 patients (7%). Amiodarone-10/42 (23.8%) followed by amitriptyline-9/42 (21.4%) and chlorpheniramine-7/42 (16.7%) was the most frequently prescribed inappropriate drug according to the first list of Beers Criteria 2003. Inappropriate drugs identified according to the second list of Beers criteria were aspirin and clopidogrel in bleeding-3/42 (7.1%) followed by calcium channel blockers amlodipine-1/42 (2.4%) and diltiazem-1/42 (2.4%) in constipation and citalopram in hyponatremia-1/42 (2.4%). Predicators were polypharmacy (odds ratio (OR) – 4.85; 95% confidence interval (CI), 4.27–5.44), advanced age (>70 years) (OR – 1.43; 95%CI, 1.35–1.50) and increased hospital stay (OR – 1.20; 95%CI, 1.13–1.26).

Conclusions: The lower prevalence of inappropriate drug use in Indian elderly inpatients demonstrates that the provision of unbiased information to the clinicians on a sustained basis can lead to better prescribing.

687. Type 2 Diabetes Among Adults in Bangladesh: A Population-based Study

Muhammad AB Chowdhury,[1] Hafiz MRU Khan,[1] Md Jamal Uddin,[2] Md Rabiul Haque[3]. *[1]Department of Biostatistics, Robert Stempel College of Public Health and Social Work, Florida International University, Miami, FL, USA; [2]Department of Statistics, Shahjalal University of Science and Technology, Sylhet, Bangladesh; [3]Department of Population Sciences, University of Dhaka, Dhaka, Bangladesh.*

Background: Diabetes is one of the most prevalent non-communicable diseases in Bangladesh. However, risk factors for diabetes among adult patients in Bangladesh remain unknown.

Objectives: The study aimed to determine the risk factors for type 2 diabetes among adult population of Bangladesh.

Methods: We conducted a cross-sectional study using data from the nationally representative Bangladesh Demographic and Health Survey. A random sample of adults aged 35 years and older from both urban and rural areas who participated in the survey were included. Diabetes mellitus was defined by a fasting plasma blood glucose level of ≥7 mm/L. Hypothesized factors associated with diabetes included age, sex, education, place of residence, social status, and body mass index (BMI). Logistic regression model was used to identify factors associated with diabetes.

Results: We found age, education, socioeconomic status, place of residence (rural or urban), regions of residence, overweight and obesity, and elevated blood pressure as the important risk factors of diabetes. Age group 55–59 years had the maximum likelihood to have the diabetes (OR = 2.27, CI: 1.66–3.12) than the age group 35 years and older. Moreover, respondents who had higher educational attainment (OR = 1.45, CI: 1.01–2.10) and highest social status (OR = 2.00, CI: 1.48–2.72) had higher odds of having diabetes than respondents with no education and lowest social status, respectively. The odds of diabetes between male and female was not significantly different (OR = 0.79, CI: 0.60–1.03).

Conclusions: In this study of adults from Bangladesh, increasing age, higher socioeconomic status, hypertension, and obesity were important factors associated with diabetes mellitus. Immediate steps should be taken for early diagnosis, awareness, and health education programs for changing lifestyles to reduce the risk of diabetes in Bangladesh.

688. Risk Factors of Hypertension Among Adults in Bangladesh: Evidence from a National Cross Sectional Survey

Muhammad AB Chowdhury,[1] Md Jamal Uddin,[2] Boubakari Ibrahimou,[1] Md Rabiul Haque,[3] Oren Dale Williams.[1] *[1]Department of Biostatistics, Robert Stempel College of Public Health and Social Work, Florida International University, Miami, Florida, United States; [2]Department of Statistics, Shahjalal University of Science and Technology, Sylhet, Bangladesh; [3]Department of Population Sciences, University of Dhaka, Dhaka, Bangladesh.*

Background: Hypertension is an increasing problem in South Asia, particularly Bangladesh. Although some epidemiological studies on hypertension have been conducted in Bangladesh, the prevalence and risk factors of hypertension in this nation remain unknown.

Objectives: The study aimed to determine the prevalence and risk factors of hypertension among adult population in Bangladesh.

Methods: We conducted a cross-sectional study using data from the nationally representative Bangladesh Demographic and Health Survey. Adults aged 35 years and older who participated in the survey were eligible for inclusion. Hypertension was defined by a systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or receipt of an antihypertensive medication. Hypothesized factors associated with hypertension included age, gender, social status, place of residence, and body mass index (BMI). Logistic regression models were used to determine the risk factors of hypertension.

Results: The prevalence of hypertension was 26.4% (male – 20.3%, female – 32.4%). Hypertension was significantly associated with age, education, social status, place of residence (urban or rural), body mass index (BMI), and having diabetes. For example, the likelihood of hypertension was more than four times higher (OR = 4.24, 95%CI: 3.38–5.31) among the higher aged respondents 55–59 years compared with respondents aged 35–39 years. Moreover, individuals from highest income (OR = 2.04, 95%CI: 1.63–2.54) and higher BMI (OR = 2.92, 95%CI: 2.10–4.04) had the maximum likelihood of having hypertension than the individuals with the lowest income and normal BMI, respectively.

Conclusions: The prevalence of hypertension is high (>26%) in Bangladesh. In this-cross sectional study, increasing age, higher income, and obesity were important factors of hypertension. Therefore, health education programs for changing lifestyles to reduce the risk of hypertension are required in Bangladesh.

689. Uniform vs. All-available Look-backs to Identify Exclusion Criteria in Observational Cohort Studies

Mitchell M Conover,[1] Michele Jonsson Funk[1]. [1]*Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: In cohort studies using secondary data, conventional methods characterize subjects using a uniform baseline window (look-back) for all subjects. However, Brunelli *et?al*. (PDS 2013) reported using all available covariate history to identify and adjust for confounders, which was superior to uniform look-backs in most cases examined.

Objectives: The study aimed to compare bias and efficiency of two approaches (uniform and all-available) to identifying exclusion criteria.

Methods: We simulated dichotomous confounder (C), exposure (E), outcome (D), and 120-month history of healthcare encounters and insurance status (database enrollment). We also simulated an unmeasured confounder (F) causally associated with all study variables and causally linked database enrollment to healthcare visits. In addition to a crude analysis with no exclusions, we identified and excluded subjects with C using uniform and all-available look-backs. We varied model parameters and variable relationships in multiple scenarios, conducting 1000 iterations with study sizes of 5000. We estimated relative bias and relative mean squared error (MSE) as all-available/uniform.

Results: With no unmeasured confounding, enrollment and visit history were similar between exposure groups. In these scenarios, relative bias ranged from 0.04 to 0.70 and relative MSE from 0.21 to 1.34. All-available look-back was always less biased but was in some cases less precise. With unmeasured confounding (F), enrollment and visit history varied by exposure group. In one scenario, median enrollment and visit history were 22 months and seven visits among the exposed and 16 months and three visits among the unexposed. When C and F acted in the same direction, relative bias ranged from 0.44 to 0.97 and relative MSE from 0.31 to 0.99. When C and F acted in opposite directions, the crude usually outperformed all adjustment methods.

Conclusions: The all-available approach results in the best control of the measured confounder C but may be less precise due to additional exclusions. It produces the least biased estimates in all cases examined except when residual confounding due to misclassification of C offsets unmeasured confounding acting in the opposite direction.

690. Length of Comorbidity Lookback Period and Predicting One-Year Mortality Based on Registry Data from Denmark

Morten Madsen,[1] Vera Ehrenstein,[1] and Henrik T Sørensen[1] [1]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: To assess prognostic comparability of contrasted groups, pharmacoepidemiologists often use the Charlson Comorbidity Index (CCI) calculated using

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automated databases, such as the Danish National Registry of Patients (DNRP). Longer lookback periods identify more patients but may also capture diagnoses that are old and therefore less relevant for prognosis.

Objectives: The aim of this study was to evaluate whether length of lookback period is associated with the ability of CCI to predict 1-year mortality.

Methods: We included patients with first-time myocardial infarction (MI) in Denmark, in 2009–2011, and computed CCIs with 1, 2, 3, 4, 5, 10, 15 and 30 years' lookback period based on the DNRP. These CCIs were compared with respect to their ability to predict 1-year mortality in a Cox regression model. Data on deaths were linked from the Danish Civil Registration System. Predictive ability was measured with the Harrell's *C*-index in a crude model (CCI alone) as well as in a model adjusted for sex and age at MI diagnosis (represented as age and age squared).

Results: Among the 21 355 MI patients, 50% had at least one comorbidity recorded during a 30-year lookback period; 1-year mortality was 22%. For the crude model, there was monotone increase of the *C*-index with increasing lookback period (0.59, 0.62, 0.65 and 0.66 for 1, 3, 10 and 30 years). The model with only sex and age had a *C*-index of 0.73; upon inclusion of CCI, the *C*-index increased to 0.75, 0.76, 0.76 and 0.75 for 1, 3, 10 and 30 years of lookback.

Conclusions: With the CCI as the sole predictor, longer lookback period was associated with better prediction of 1-year mortality, and the first 10 years of lookback accounted for most of the predictive ability. Age and sex were better predictors of 1-year mortality than CCI, although adding CCI improved the model. As long as age, sex and CCI are accounted for, length of lookback period in the DNRP for determining the CCI was of minor importance with respect to predicting 1-year mortality.

691. Backdating of Events in Electronic Primary Care Health Data: Should One Censor at the Date of Last Data Collection

Cormac J. Sammon[1] and Irene Petersen[1] [1]*Department of Primary Care and Population Health, University College London, London, UK.*

Background: Studies carried out in UK primary care databases often censor follow-up of patients at the dates data are last collected from practices (last collection dates (LCDs)). However, given that events that occur outside a general practitioner practice are often entered into the medical record at a later date, by backdating the date of event occurrence, censoring at LCDs may result in event ascertainment becoming increasingly incomplete towards the end of data collection.

Objectives: The aim of this study was to investigate the impact of censoring at LCDs on the inclusion of backdated events in a UK primary care database.

Methods: This study utilised two versions of The Health Improvement Network (THIN), one in which the maximum LCD was 31 January 2013 (THIN13) and one in which the maximum LCD was 31 January 2014 (THIN14). By linking these datasets by practice and restricting THIN14 to events that occurred before the LCDs recorded in THIN13, THIN13 became a subset of THIN14 in which events that occurred before the THIN13 LCDs but were not recorded until after were missing. In each dataset, the total and Read code chapter specific number of events in each month prior to the THIN13 LCDs was calculated, and the difference (i.e. the number of events missing in THIN13) was expressed as a percentage of the number of events in THIN14.

Results: THIN13 contained 901 995 (0.3%) less events than THIN14. The proportion missing in THIN13 was highest in the month prior to the LCDs (9.6%), decreasing to 5.2% in the 6 months prior and 3.4% in the 12 months prior. The Read code chapter specific analysis indicated that the proportion of missing events at 1, 6 and 12 months prior to the LCDs was higher for events typically diagnosed in secondary care (e.g. 28%, 8% and 5% of cancer events; 18%, 7% and 5% of cardiovascular events) than for events that can typically be diagnosed in primary care (e.g. 2%, 1% and 1% of respiratory events; 3%, 1% and 1% of skin condition events).

Conclusions: Studies using primary care databases, particularly those investigating events diagnosed outside primary care, should consider censoring follow-up 1–12 months prior to the LCDs or risk including person time during which data are incomplete.

692. Informative Censoring Index: Quantifying the Potential for Informative Censoring in As-Treated Analyses

Wendy Camelo Castillo,[1] Til Sturmer,[2] and Michele Jonsson Funk[2] [1]*Pharmaceutical Health Services*

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Research, University of Maryland, Baltimore, MD, USA; [2]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

Background: As-treated (AT) analyses are less susceptible to bias owing to exposure misclassification than intent to treat (IT) but may induce bias owing to informative censoring of unknown magnitude and direction.

Objectives: We propose a new metric—the informative censoring index (ICI)—to quantify the magnitude of informative censoring and apply it to an analysis comparing treatments for hypertension.

Methods: We identified Medicare beneficiaries (2006–2010), ≥65 years, at high risk for cardiovascular disease, initiating an antihypertensive (angiotensin converting enzyme inhibitor [ACEI] or thiazide [TZ]) after ≥6 months without use. We estimated the cumulative risk (CR) of mortality and myocardial infarction (MI) at 6 months, and 1, 2 and 3 years after initiation separately for ACEI and TZ using Kaplan–Meier estimators adjusted for baseline confounding by propensity score weighting. We compared the IT estimates of CR with three AT approaches in which we censored for discontinuation (D), switching (S), and/or augmenting (A) the index treatment. To assess the extent of informative censoring in each AT estimate, the ICI was calculated as (CR-AT/CR-IT) within each treatment cohort at each time point, where an ICI = 1 indicated no difference between the IT and AT estimates of cumulative risk.

Results: We identified 90 493 new users (ACEI = 71%). Censoring owing to D (ACEI = 41%; TZ = 49%), S (ACEI = 9%; TZ = 6%), or A (ACEI = 14%; TZ = 12%) was common. For MI, the ICI was 0.9–1.0 in ACEI initiators for all AT analyses (suggesting little informative censoring). Among TZ initiators, the ICI varied widely from 1.0 (AT-D) to 0.7 (AT-DSA) after 1 year of follow-up. For mortality, the ICI was near 0.8 for both ACEI and TZ in AT-D and AT-DS analyses. The largest ICI decrease for both treatments occurred when censoring for augmentation.

Conclusions: The degree of informative censoring varied by outcome, duration of follow-up, censoring event, and sometimes by treatment. While performance will depend on the relative magnitude and direction of IT and AT biases, the ICI can be used to assess the extent of informative censoring without estimating the main treatment effect and thus may help to detect selection bias that is differential by treatment.

693. Apparent Treatment Effect Heterogeneity Due to Residual Confounding

Michele Jonsson Funk[1] and J Bradley Layton[1]
[1]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA.

Background: The use of interaction terms to assess treatment effect heterogeneity is considered best practice; however, this method only adjusts for the marginal associations of the confounders and thus may lead to residual confounding of the treatment effect in subgroups.

Objectives: The aim of this study was to assess the potential for residual confounding of subgroup treatment effects based on interaction terms.

Methods: We conducted two studies: (i) a simulated cohort study ($n = 200\,000$) in which the true treatment effect was under investigator control and (ii) an applied analysis of statin use (versus non-use) on acute kidney injury (AKI) in the MarketScan database. In the simulated cohort, the strength (but not direction) of the effects of some confounders on the outcome differed by subgroup (A vs. B). The true treatment effect was null (RR = 1.0) overall and in the subgroups. In the second study, the subgroup of interest was sex (male [M] vs. female [F]), and the true effect sizes were unknown. In both studies, we estimated the relative treatment effects (RR) with 95% confidence intervals (CIs) in subgroups using two modeling approaches: interaction term between treatment and subgroup and subgroup-specific models.

Results: In the simulated cohort, the crude estimate was confounded (RR = 3.1, CI: 3.0–3.4), but the overall adjusted estimate was unbiased (RR = 1.0, CI: 0.96–1.04). The subgroup estimates using interaction terms were biased (Group A: RR = 1.16, CI: 1.10–1.23; Group B: RR = 0.86, CI: 0.81–0.91), while those from the subgroup-specific models were not (Group A: RR = 1.01, CI: 0.95–1.07; Group B: RR = 0.98, CI: 0.92–1.04). In the applied analysis of claims data, the crude effect of statins on AKI was RR = 3.11 (CI: 3.04–3.17), while the adjusted estimate was RR = 0.97 (CI: 0.94–0.99). Using an interaction term between sex and statin use, the treatment effects in women and men were RR = 1.16 (CI: 1.12–1.20) and RR = 0.83 (CI: 0.80–0.85), respectively. Using sex-specific models, the treatment effects in women and men were RR = 1.09 (CI: 1.07–1.11) and RR = 0.97 (CI: 0.95–0.97), respectively.

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Conclusions: Assessment of treatment effect heterogeneity using interaction terms may be misleading when the effects of confounders differ by subgroup.

694. A Strategy for Assessing Channeling Based on Unmeasured Variables in Comparative Studies of New Drugs

Hiraku Kumamaru,[1] Robert J. Glynn,[1] Sebastian Schneeweiss,[1] and Joshua J. Gagne[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.*

Background: In studies of newly marketed medications, channeling can lead to confounding, which may or may not be addressable by measured variables. While strategies to evaluate the presence of unmeasured confounding are limited, the existence of old drug initiators before new drug market entry may provide an opportunity to assess unmeasured confounding due to channeling.

Objectives: The aims of this study were to propose a strategy for assessing unmeasured confounding due to channeling and to assess it in two studies: dabigatran versus warfarin on mortality and coxibs versus non-selective non-steroidal anti-inflammatory drugs (ns-NSAIDs) on gastrointestinal (GI) bleeds.

Methods: We formed concurrent cohorts of new and old drug initiators and historical cohorts of old drug initiators using US claims databases. We used logistic regression to estimate three odds ratios (ORs) comparing outcomes of old drug initiators in the historical versus concurrent cohort: (i) crude, (ii) pre-defined propensity score (PS)-decile stratified, and (iii) high-dimensional PS (hdPS)-decile stratified. Under the assumption that the new drug is a viable alternative for the old drug, we expect an OR of 1 in the absence of channeling based on unmeasured factors. Deviations from 1 would indicate unadjusted confounding.

Results: Concurrent warfarin initiators were older and sicker than historical warfarin initiators. The 180-day mortality was 2.4% in the concurrent versus 2.1% in the historical cohort (crude OR, 1.11 [95% confidence interval, 0.85–1.44]). ORs were 0.92 [0.71–1.20] in PS-stratified and 0.92 [0.70–1.20] in hdPS-stratified analyses. As compared with historical ns-NSAID initiators, concurrent initiators had similar mean age and comorbidity distributions, but slightly lower GI bleed incidence (0.6% vs. 0.7%). The crude OR was 0.83 [0.62–1.12]; PS-stratified and hdPS-stratified ORs were 0.81 [0.60–1.10] and 1.03 [0.68–1.56], respectively.

Conclusions: In two examples, ORs from hdPS-stratified analyses comparing outcomes of older drug initiators in the concurrent and historical cohorts were close to the null. While this does not guarantee absence of unmeasured confounding in the comparison between concurrent new and old drug initiators, it is a necessary condition for it.

695. Use of Drugs for ADHD in the Adult Population of the Nordic Countries During 2008–2012

Øystein Karlstad,[1] Helga Zoega,[2] Kari Furu,[1] Jaana Martikainen,[3] Shahram Bahmanyar,[4] Helle Kieler,[4] and Anton Pottegård[5] *[1]Department of Pharmacoepidemiology, Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway; [2]Centre of Public Health Science, University of Iceland, Reykjavik, Iceland; [3]Research Department, The Social Insurance Institution, Helsinki, Finland; [4]Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [5]Clinical Pharmacology, Department of Public Health, University of Southern Denmark, Odense, Denmark.*

Background: Attention deficit hyperactivity disorder (ADHD) is a common disease in adolescence and has been recognized as a disease that can persist into adulthood. ADHD drugs have only recently been approved for treatment of adults, and guidelines have mainly focused on diagnosis and treatment of children and adolescents.

Objectives: The aim of this study was to assess the use of ADHD drugs among adults 18–44 years old in the five Nordic countries during 2008–2012, comprising ~9 million inhabitants.

Methods: Data on ADHD drugs dispensed from pharmacies were drawn from the complete prescription registers covering all inhabitants in each Nordic country (Denmark, Finland, Iceland, Norway and Sweden). ADHD drugs were methylphenidate, atomoxetine, amphetamine and dexamphetamine. Data were pooled in one database and analysed as annual cross-sections for 2008–2012. Period prevalence was defined as number of users of drugs per year, while incidence was number of new users per year (730-day run-in). Denominator was the gender-specific and age-specific population of same year. Among prevalent users of ADHD drugs

in each year, concurrent use of other psychotropics was measured in the same year.

Results: In 2008, 26 662 adults who are 18–44 years old (0.30% of the age-specific Nordic population) used ADHD drugs, increasing to 63 811 (0.71%) in 2012. Increasing prevalence was observed in both genders and all age groups. The male/female prevalence ratio was 1.37 in 2008 and decreased to 1.20 in 2012. Incidence increased from 0.11% to 0.20% during the study period. Both prevalence and incidence were highest in the youngest adults and decreased by age. Extended-release methylphenidate was the most frequently used ADHD drug; 58% of users of ADHD drugs concurrently used other psychotropic drugs. Antidepressants (36%) were most frequently used, followed by hypnotics (25%), anxiolytics (18%), antipsychotics (18%) and antiepileptics (14%). Early discontinuation and switch in ADHD treatment will be analysed later.

Conclusions: Use of ADHD drugs in the adult population of the Nordic countries more than doubled during the study period. The adults using ADHD drugs frequently received drugs for treatment of other psychiatric conditions.

696. Factors Associated with Pharmacological Treatment Initiation in Adult Attention-Deficit/Hyperactivity Disorder Patients: Findings from a Publicly Insured Population

Yan Li,[1] Wei Liu,[1] Paul Kubilis,[1] Yanmin Zhu,[1] and Almut G. Winterstein[1,2] *[1]Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA; [2]Department of Epidemiology and Biostatistics, College of Public Health and Health Professionals and College of Medicine, University of Florida, Gainesville, FL, USA.*

Background: Attention-deficit/hyperactivity disorder (ADHD) in adulthood adversely affects occupational, academic, and social functioning but can be effectively managed by medications. Factors associated with ADHD pharmacological treatment initiation in children and adolescents are well described, while little is known for adults.

Objectives: The aim of this study was to explore how patient socio-demographic and clinical characteristics affect ADHD pharmacological treatment initiation.

Methods: Using the US Medicaid eXtract Files of 29 states from 1999 and 2010, we assembled a retrospective cohort of adult patients with new ADHD episodes. The outcome of interest was initiation of stimulants or atomoxetine within 6 months after the index diagnosis. Treatment initiators and non-initiators were compared with respect to their baseline socio-demographics, mental comorbidities, history of psychotropic use, and diabetes and cardiovascular conditions using multivariable logistic regression.

Results: Of the 32 622 eligible ADHD patients, 8601 (26.4%) started pharmacological treatment within 6 months of diagnosis. Female (OR 1.46; 95%CI 1.38–1.54), White (OR 1.61; 95%CI 1.51–1.71), and patients aged >25 years (OR 1.61; 95%CI 1.51–1.71) were more likely to initiate therapy. More than 70% of the study population had one or more diagnoses for mental disorders in the year prior to the new ADHD episode. The presence of more severe conditions including schizophrenia (OR 0.61; 95%CI 0.54–0.69) and bipolar disorders (OR 0.90; 95%CI 0.84–0.97) decreased the probability of initiation, while the presence of anxiety (OR 1.17; 95%CI 1.09–1.25) and substance use disorders (OR 1.17; 95%CI 1.08–1.27) increased the probability. Pre-existing cardiovascular disease (OR 0.79; 95%CI 0.73–0.86) and diabetes (OR 0.66; 95%CI 0.58–0.74) were adversely associated with treatment initiation.

Conclusions: Several socio-demographic and clinical characteristics were associated with the initiation of ADHD medications in adult patients. The findings provide valuable information to future efforts of providing timely and appropriate pharmacological treatment to these patients.

697. Medication Discontinuation in Patients After Discharge from a Psychiatric Hospital

Heshu Abdullah-Koolmees,[1,2,5] Helga Gardarsdottir,[1,3] Dilek Yazir,[1] Lennart J. Stoker,[2] Judith Vuyk,[4] Toine C. G. Egberts,[1,3] and Eibert R. Heerdink[1,3,4] *[1]Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands; [2]Department of Clinical Pharmacy, Brocacef Ziekenhuisfarmacie, Maarssen, Utrecht, The Netherlands; [3]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands; [4]Division of Willem Arntz, Altrecht Institute for Mental Health Care, Utrecht, The Netherlands; [5]Department of Pharmacy, Diakonessenhuis, Utrecht, The Netherlands.*

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Background: Patients discharged from a psychiatric hospital may be at risk for intentional or unintentional discontinuation of their medication.

Objectives: The aim of this study was to assess discontinuation and other medication changes in use of psychiatric and/or somatic medication after discharge from a psychiatric hospital.

Methods: A retrospective, follow-up study was conducted in patients discharged from four psychiatric hospitals in the Netherlands between 2006 and 2009. Patients' medication used during the last 2 days of hospitalization was compared with medication dispensed during the 3 months after discharge. Changes in psychiatric and somatic medication use were investigated; medication changes were defined as discontinuation, start, or switch. When medication dispensed after discharge was unchanged, then patients were classified as continuers. Relative risks (RR) with 95% confidence intervals (95%CIs) of discontinuation were estimated using Cox regression analysis.

Results: A total of 1324 patients were included of which 69.8% discontinued and 9.7% switched one or more medications; 47.4% started a medication, which was not dispensed during the last 2 days of hospitalization; and 13.7% continued all medication after discharge without a discontinuation or change at all. In the 644 patients using antipsychotics, 25.2% discontinued. Of 292 patients using cardiovascular medications, 28.4% discontinued. RR for discontinuation of a medication was highest in patients using as-needed medication prior to discharge (RR = 1.85, 95%CI = 1.55–2.20).

Conclusions: Discharge from a psychiatric hospital was accompanied with medication discontinuation in almost 70% of the patients. Discontinuation of somatic medication was more frequent than psychiatric medication. Medication discontinuation can be intentional, but it seems unlikely that about a quarter of antipsychotics and cardiovascular medications are discontinued, which are used chronically. More research is needed to assess if these medication discontinuations are intentional or unintentional and its consequences for patients' overall health.

698. Restless Legs Syndrome: Epidemiology and Treatment

Ju Hyeun Kim,[1] Adel Alrwisan,[1] Haesuk Park,[1] and Abraham G. Hartzema[1] [1]*Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA.*

Background: Publicity surrounding restless legs syndrome (RLS) has increased since the approval in the mid-2000s of several medications with an indication for RLS treatment. The increase in RLS research is also expected to heighten awareness and consequently diagnosis and treatment.

Objectives: The objective of this study was to assess the yearly prevalence and trend of physician diagnosed RLS, and commonly used medications for RLS.

Methods: A retrospective analysis of the Truven Health Analytic data was conducted from 2008 to 2012 for individuals 18 years of age or older. RLS was captured with diagnosis code from inpatient and outpatient data. The yearly prevalence rates for RLS between 2008 and 2012 were estimated and adjusted for age and gender. The proportions of subjects with RLS who received ropinirole, pramipexole, gabapentin, or pregabalin were assessed.

Results: An average of 27 million subjects per year were included in the analysis. The crude prevalence for RLS increased each year between 2008 and 2012 and doubled from 48 to 112 cases per 100 000 persons. The age-standardized RLS prevalence ratios comparing 2012 with 2008 were 2.53 for men and 2.41 for women. In both genders, RLS prevalence increased with age, peaking at age 70–80 years. Across all years, women were more likely to be diagnosed with RLS compared with men with a ratio up to 2.01. In 2008, 46.6% of RLS patients received any RLS treatment, and the proportion was 46.5% in 2012. Among RLS subjects who received any RLS treatment in 2008, 50.9% were on ropinirole, 36.8% on pramipexole, 22.5% on gabapentin, and 11.3% on pregabalin. In 2012, the rates were 48.8%, 35.5%, 31.5%, and 7.9%, respectively. A higher proportion of subjects on dopamine receptor agonists (ropinirole and pramipexole) also had Parkinson's disease (8.4–8.7%), compared with those receiving gabapentin (3.1%) or pregabalin (2.3%).

Conclusions: Between 2008 and 2012 in the USA, the prevalence of RLS among adults increased. Women and elderly were more likely to be diagnosed with RLS across all the study years. However, with the exception of gabapentin, the prevalence of RLS

treatment did not increase during the same time period.

699. Trends in Prescribing of Antidepressants for Depression and Off-Label Indications

Jenna Wong,[1] Aude Motulsky,[2] and Robyn Tamblyn[1]
[1]*Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada;* [2]*Faculty of Medicine, McGill University, Montreal, QC, Canada.*

Background: Antidepressants are increasingly prescribed for nondepressive disorders and nonapproved (off-label) indications, but the magnitude of this phenomenon is unknown.

Objectives: The aim of this study was to determine how prescribing of antidepressants for depression and off-label indications has changed over time.

Methods: Data from a primary care electronic prescribing system in Canada were used to identify antidepressant prescriptions written between January 2006 and December 2012 for community-based adults. For each drug, physicians had to document the indication via a drop-down menu or free-text field. On-label indications included Health Canada or FDA-approved indications. All other indications were considered off label, and their level of scientific evidence was assessed using the DrugDex compendium. Binomial regression was used to estimate 5-year risk differences (RD) in prescribing of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitor (SNRIs), tricyclic antidepressant (TCAs), and other antidepressants (bupropion, mirtazapine, and trazodone) for depression and off-label indications. All models adjusted for patient age, sex, comorbidities, and location and accounted for patient clustering using generalized estimating equations.

Results: Among 73 351 prescriptions for 16 669 adults, 56% were for depression, 15% were for approved, nondepressive indications, and 30% were for off-label indications. Among off-label prescriptions, the top indications were anxiety (35%), sleep disorders (33%), and pain (17%), and 94% were for indications that were not strongly evidence based. Over time, prescribing for depression decreased for SNRIs (5-year RD −12%; 95%CI −13% to –9%) and SSRIs (RD −7%; –8% to −5%) and increased for other antidepressants (RD 9%; 7% to 11%). No trends were observed with TCAs. For off-label indications, prescribing increased for SSRIs (RD 4%; 2% to 5%), SNRIs (RD 2%; 0.2% to 3%) and TCAs (RD 4%; 2% to 7%) and decreased for other antidepressants (RD −8%; –10% to −6%). Trends were similar among new prescriptions.
Conclusions: We found that nearly half of antidepressant prescriptions are for nondepressive disorders and that SSRIs, SNRIs, and TCAs are being increasingly prescribed for off-label indications without strong scientific evidence.

700. Initiation and Duration of Selective Serotonin Reuptake Inhibitor Prescribing Over Time: A UK Cohort Study

Rachel L. McCrea,[1] Cormac J. Sammon,[1] Irwin Nazareth,[1] and Irene Petersen[1] [1]*Department of Primary Care and Population Health, University College London, London, UK.*

Background: Recent media reports in the UK have focussed on the 'staggering' rise in the numbers of antidepressant prescriptions being issued in England. This rise does not appear to reflect an increase in the prevalence of depression. Some have suggested that it reflects an increase in the numbers of people taking antidepressants long term. We sought to explore this further, focussing on prescriptions of selective serotonin reuptake inhibitors (SSRIs).

Objectives: The aims of this study were (i) to examine the rate of initiation of SSRIs over time and the sociodemographic factors associated with initiation and (ii) to examine changes over time in the duration of prescribing episodes.

Methods: We analysed data from 7 025 802 individuals included in The Health Improvement Network primary care database who were registered with a general practitioner (family doctor) between 1995 and 2012. Poisson regression was used to explore the factors associated with SSRI initiation.

Results: The rate of SSRI initiation increased from 1.03 per 100 person years in 1995 to 2.15 in 2001 but remained relatively constant from then to 2012. Women were more than twice as likely as men to initiate an SSRI during follow-up (adjusted rate ratio 2.14, 95%CI: 2.13, 2.15). For both men and women, the SSRI initiation rate was lowest in the 60–79 age

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band. For men, the rate of SSRI initiation was highest in those aged 80 or over (adjusted rate ratio compared with those aged 18–39: 1.29, 95%CI: 1.25, 1.34). For women, the rate of SSRI initiation was highest in those aged 18–39—women in the 60–79 age range were nearly half as likely to initiate an SSRI as those in the 18–39 age range (rate ratio: 0.55, 95%CI: 0.54, 0.57),

The median duration of prescribing episodes increased from 112 days in 1995 to 169 days for episodes starting in 2010.

Conclusions: Despite the reports in the media describing the soaring rate of antidepressant prescribing, there has been no similar continued increase in the rate of SSRI initiation over time. However, our results suggest that individuals who take SSRIs are receiving treatment for longer.

701. Pregnancy Outcome in Women Treated with Adalimumab for Rheumatoid Arthritis: An Update on the OTIS Autoimmune Diseases in Pregnancy Project

Christina D. Chambers,[1,2] Diana L. Johnson,[1] Yunjun Luo,[1] Ronghui Xu,[2,3] and Kenneth L. Jones[1] *[1]Department of Pediatrics, University of California San Diego, La Jolla, CA, USA; [2]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA; Department of [3]Mathematics, University of California San Diego, La Jolla, CA, USA.*

Background: Adalimumab (ADA) is a monoclonal antibody to tumor necrosis factor alpha approved for several indications including rheumatoid arthritis (RA).

Objectives: The aim of this study was to estimate the risk of birth defects and other adverse pregnancy outcomes in women exposed to ADA for RA compared with disease-matched (DM) and healthy comparison (HC) women.

Methods: Between 2004 and 2013, the OTIS Collaborative Research Group conducted a North American prospective cohort study of pregnancy outcomes in women with ADA for RA compared with DM and HC women. Women were recruited before 20 weeks' gestation and followed up by multiple telephone interviews and medical record review. A subset of live born infants received a dysmorphological exam by a study physician. Outcomes were compared using multivariable regression and survival methods.

Results: A total of 74 ADA, 80 DM, and 218 HC women were enrolled; 5.9% were lost to follow-up. All ADA women were exposed in the first trimester; approximately 43% used ADA in all trimesters. Disease severity was similar between the disease groups. The rate of major defects in the ADA, DM, and HC groups was 5.6%, 7.8%, and 5.5%, respectively. In adjusted analysis, there was no significant difference in the rate of major malformations among live births in the ADA versus DM groups (adjusted relative risk 1.14, 95% confidence interval (CI) 0.26, 4.93). No pattern of minor malformations was identified in the ADA group. Using Cox modeling, the adjusted hazard ratio (aHR) for ADA compared with DM for spontaneous abortion was 1.96 (95%CI 0.47, 8.26); the rate was elevated compared with the HC group (aHR 3.79, 95%CI 1.01, 14.23), although the number of events was small. The rate of preterm delivery did not differ significantly among groups, nor did the proportion of infants who were small for gestational age.

Conclusions: Women treated with ADA for RA during the first trimester compared with DM without ADA do not appear to be at increased risk for the adverse pregnancy outcomes evaluated. Although the sample size is small, the results provide reassurance to pregnant women with RA who require treatment with ADA.

702. Metformin Use in Pregnancy and Risks of Birth Defects

Carla M. Van Bennekom,[1] Stephanie E. Dukhovny,[2] Sonia Hernandez-Diaz,[3] Martha M. Werler,[1,4] Marlene Anderka,[5] David R. Gagnon,[6] and Allen A. Mitchell[1] *[1]Slone Epidemiology Center, Boston University, Boston, MA, USA; [2]Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, OR, USA; [3]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA; [4]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; [5]Massachusetts Department of Public Health, Boston, MA, USA; [6]Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA.*

Background: Diabetes is a common complication of pregnancy. Poor control is associated with maternal and neonatal morbidity, including increased risks for birth defects. Risks decrease with improved glucose control. Oral hypoglycemic agents are first-line

treatment for diabetes in non-pregnant patients, but use in pregnancy (largely metformin) is controversial.

Objectives: The aim of this study was to identify associations between metformin use and major birth defects.

Methods: We used 1997–2009 data from the National Birth Defects Prevention Study, a population-based, case–control study, to assess the association between maternal first trimester metformin use for diabetes and risks for specific major birth defects. We calculated crude odds ratios and 95% confidence intervals (CIs) by exact logistic regression and, where numbers permitted (for example, heart defects and oral clefts), adjusted odds ratios and CIs using inverse probability weighting to control for potential confounders. Confounding by diabetes was assessed by comparing metformin with both insulin use in diabetic women and metformin use for infertility in non-diabetic women.

Results: Among 9355 controls, first trimester exposure prevalences of metformin for diabetes, insulin for diabetes, and metformin for infertility were 0.1%, 0.4%, and 0.3%, respectively. Compared with non-diabetic women with no metformin use, diabetic metformin users had elevated odds ratios (ORs) for heart defects, oral clefts, neural tube defects, and limb defects; these ORs were similar to those for insulin users. In contrast, metformin users for infertility had ORs of ~1.0 with the exception of limb defects, where the ORs for metformin-diabetes, insulin, and metformin-infertility, respectively, were 4.1 (1.1–12.5), 5.1 (2.7–9.2), and 2.9 (1.2–6.2).

Conclusions: As expected, insulin-dependent diabetes was strongly associated with a number of defects. For metformin, we could only partially adjust for diabetes severity. However, for most defects studied, there was no evidence that metformin is itself teratogenic, as risks were not elevated when used for a non-diabetic indication. The elevated risk for limb defects associated with metformin is a new finding, which may be due to chance, and requires further study.

703. ACE Inhibitors During the First Trimester of Pregnancy and the Risk of Congenital Malformations: A Cohort Study

Brian T. Bateman,[1,2] Sonia Hernandez-Diaz,[3] Elisabetta Patorno,[1] Rishi Desai,[1] and Krista F. Huybrechts[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.*

Background: Angiotensin-converting enzyme inhibitors (ACEi) are commonly used medications for the treatment of hypertension in women of reproductive age. The available literature is inconsistent regarding their teratogenic potential.

Objectives: The aim of this study was to examine the association between first trimester ACEi exposure and the risk for major congenital malformations (overall), cardiac malformations, and central nervous system (CNS) malformations.

Methods: We used a cohort of 44 716 women with chronic hypertension who had completed pregnancies linked to liveborn infants derived from Medicaid claims from 2000 to 2007. We examined the risk of malformations associated with first trimester exposure to an ACEi, which was defined based on a filled outpatient prescription during this window. The reference group consisted of pregnancies with untreated hypertension. Stratification on a high-dimensional propensity score (100 strata of fixed score width) was used to control for potential confounders including maternal demographics, obstetric and medical conditions, exposure to other medications, and 100 empirically identified covariates.

Results: There were 1900 (4.2%) women dispensed an ACEi during the first trimester. The risk of malformations (overall) in the ACEi exposed was 7.7% versus 4.4% in the non-exposed, cardiac malformations 5.0% versus 2.0%, and CNS malformations 0.21% versus 0.17%. After controlling for confounders, through high-dimensional propensity score stratification, the RR for malformation (overall) was 1.00 (95%CI, 0.83 to 1.21), for cardiac malformations 0.99 (95%CI, 0.77 to 1.27), and for CNS malformations 1.04 (95%CI, 0.28 to 3.86). Results were similar when the reference group was women treated with other (non-ACEi) antihypertensives during the first trimester.

Conclusions: After accounting for confounders, exposure to an ACEi during the first trimester was not associated with an increased risk of malformations

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(overall), cardiac malformations, or CNS malformations, although the last association was imprecisely estimated.

704. Late Pregnancy Exposure to Beta Blockers and the Risks of Neonatal Hypoglycemia and Bradycardia

Brian T. Bateman,[1,2] Krista F. Huybrechts,[1] Rishi Desai,[1] Elisabetta Patorno,[1] and Sonia Hernandez-Diaz[3]
[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA.

Background: Beta blockers are widely used in the treatment of hypertension during pregnancy. These medications cross the placenta and may cause physiologic changes in neonates exposed *in utero*. Some prior studies suggest an association between late pregnancy beta blocker exposure and the risks of neonatal hypoglycemia and bradycardia, but the magnitude of these risks and the question of whether they extend to the alpha-beta blocker labetalol are poorly defined.

Objectives: The aim of this study was to define the risk of neonatal hypoglycemia and bradycardia associated with late pregnancy exposure to beta blockers.

Methods: We used a cohort of 2 292 116 completed pregnancies linked to liveborn infants of women enrolled in Medicaid from 2003 to 2007. We examined the risk of neonatal hypoglycemia and neonatal bradycardia associated with maternal exposure to beta blockers at the time of delivery, defined by an outpatient dispensing whose days supply overlaps with the date of delivery. The reference group consisted of pregnancies not exposed at the time of delivery. Propensity score matching (1:3 fixed ratio) was used to control for potential confounders including maternal demographics, obstetric and medical conditions, and exposure to other medications.

Results: There were 10 585 (0.5%) pregnancies exposed to beta blockers at the time of delivery. The risk of neonatal hypoglycemia was 4.3% in the beta blocker exposed versus 1.2% in the unexposed; the risk of neonatal bradycardia was 1.6% in the exposed versus 0.5% in the unexposed. After controlling for confounders, risk remained elevated for both neonatal hypoglycemia and bradycardia among exposed pregnancies versus unexposed (aOR 1.7, 95%CI 1.5 to 1.9 and aOR 1.3, 95%CI 1.1 to 1.6, respectively). Risks were similarly elevated for those exposed to labetalol versus unexposed (aOR 1.8, 95%CI 1.6 to 2.0 for hypoglycemia and 1.3, 95%CI 1.1 to 1.7 for bradycardia). Results were similar across sensitivity analyses.

Conclusions: Our findings suggest that neonates born to mothers exposed to beta blockers in late pregnancy, including labetalol, are at elevated risk for neonatal hypoglycemia and bradycardia. Exposed neonates may benefit from monitoring for these conditions.

705. Ondansetron for the Treatment of Nausea and Vomiting of Pregnancy and the Risk of Birth Defects

Carla M. Van Bennekom,[1] Samantha E. Parker,[1] Marlene Anderka,[2] Carol Louik,[1] and Allen A. Mitchell[1] *[1]Slone Epidemiology Center, Boston University, Boston, MA, USA; [2]Massachusetts Department of Public Health, Boston, MA, USA.*

Background: The off-label use of ondansetron for the treatment of nausea and vomiting during pregnancy (NVP) has been increasing. Earlier studies, including a National Birth Defects Prevention Study (NBDPS) analysis for 1997–2004, have observed elevated risks for some birth defects, but the numbers of exposures were small. Information regarding the safety of its use is inadequate.

Objectives: The aim of this study was to identify trends in first-trimester ondansetron use for NVP and associations between such use and specific birth defects.

Methods: We used data from two case–control studies, the Slone Birth Defects Study (BDS) (1997–2013) and the NBDPS (2005–2009; data subsequent to the earlier study), to assess maternal first-trimester ondansetron use for NVP and the risk of selected major birth defects. To measure these associations, we calculated adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The prevalence of ondansetron use among controls increased from 0% to 6.7% in BDS ($n = 243$) and from 2.6% to 7.2% in NBDPS ($n = 111$) during the respective study periods. Previously identified risks for specific defects were not supported in either

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data set, with the possible exception of cleft palate, which was modestly elevated (OR: 1.5; CI: 0.9, 2.5) in the NBDPS but decreased (OR: 0.4; CI: 0.2, 0.8) in the BDS data. On the other hand, in BDS, use was associated with a modestly increased risk of renal agenesis/dysplasia (OR: 2.3; CI: 1.3, 4.0), and in NBDPS, risks were modestly increased for hypoplastic left heart syndrome (OR: 1.5; CI: 0.7, 3.1), and diaphragmatic hernia (OR: 1.7; CI: 0.9, 3.5).

Conclusions: Despite the rapid increase in use of ondansetron, the number of exposed cases in the current data was small, and risk estimates were unstable; given the current widespread use of ondansetron, further studies of its risk and safety are needed.

706. Pregnancy Outcome in Women Treated with Etanercept: An Update on the OTIS Autoimmune Diseases in Pregnancy Project

Christina D. Chambers,[1,2] Diana L. Johnson,[1] Yunjun Luo,[1] Ronghui Xu,[2,3] and Kenneth L. Jones[1] *[1]Department of Pediatrics, University of California San Diego, La Jolla, CA, USA; [2]Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA; [3]Department of Mathematics, University of California San Diego, La Jolla, CA, USA.*

Background: Etanercept (ETA) is an anti-tumor necrosis factor medication indicated for the treatment of certain inflammatory diseases.

Objectives: The aim of this study was to estimate the risk of adverse pregnancy outcomes in women exposed to ETA compared with disease-matched (DM) women.

Methods: Between 2005 and 2012, the OTIS Collaborative Research Group conducted a North American prospective cohort study of pregnancy outcomes in women treated with ETA compared with DM women. Women were followed up with multiple telephone interviews and medical record review. Disease severity was measured by maternal questionnaire. Infants were followed up for up to 1 year; development was evaluated with the Ages and Stages Questionnaire (ASQ). Outcomes were compared using multivariable regression and survival methods.

Results: A total of 370 ETA and 164 DM women were enrolled; 3.2% were lost to follow-up. A total of 344 women received ETA in the first trimester; and 51% used ETA in the third trimester. Disease severity scores were similar in the ETA and DM groups. The rates of major birth defects in live born infants in the ETA and DM groups were 9.4% and 3.5%, respectively (adjusted odds ratio 2.77, 95% confidence interval [CI] 1.04,7.35). There was no specific pattern of major birth defects identified in the ETA group. Using Cox modeling to compare ETA with DM groups, the adjusted hazard ratio (aHR) for spontaneous abortion was 0.47 (95%CI 0.20,1.12); the aHR for preterm delivery was 1.60 (95%CI 0.86,2.98). There were no significant differences between groups in prenatal or postnatal growth, rates of serious or opportunistic infections, or developmental concerns on the ASQ. No malignancies were reported.

Conclusions: The proportion of infants with major birth defects was higher in the ETA group compared with DM group. However, biologic plausibility of a drug-related effect is not supported owing to the lack of a pattern of defects and the expected minimal placental transfer of ETA in early pregnancy. There was no evidence of an increased risk for other study outcomes. Further research is required to determine if unmeasured confounding may account for differences between groups.

707. Incidence and Determinants of Fall-Related Major Bleeding Among Older Adults with Atrial Fibrillation

John A. Dodson[1,2], Andrew Petrone[1,3], David R. Gagnon[1,4], Mary E. Tinetti[5], Harlan M. Krumholz[6,7], and J. Michael Gaziano[1,3] *[1]Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), US VA Cooperative Studies Program, Boston, MA, USA; [2]Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY, USA; [3]Division of Aging, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA; [4]Biostatistics Department, Boston University School of Public Health, Boston, MA, USA; [5]Section of Geriatrics, Department of Medicine, Yale University School of Medicine, New Haven, CT, USA; [6]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA; [7]Department of Health Policy and Administration, Yale School of Public Health, New Haven, CT, USA.*

Background: Fall-related major bleeding is a concern among clinicians who are hesitant to prescribe oral anticoagulation to older adults with atrial fibrillation.

Objectives: The aim of this study was to describe the incidence and risk factors of this outcome in large datasets.

Methods: We created a retrospective cohort of 33 732 veterans with atrial fibrillation aged ≥75 years who were new referrals to VA anticoagulation clinics (warfarin therapy) between 1 January 2001 and 31 December 2012. Patients with comorbid conditions requiring warfarin (mechanical heart valve, pulmonary embolus) were excluded. Clinical characteristics, laboratory, and pharmacy data were extracted from the VA electronic medical record. We then linked VA data with Medicare claims data for subsequent hospitalizations. The primary outcome (fall-related major bleeding) was defined as any hospitalization for traumatic intracranial bleeding, hemarthrosis, or fracture-related bleeding. Cox proportional hazards regression was used to determine predictors of interest selected *a priori* based on prior known associations.

Results: Mean patient age was 81.1 ± 4.1 years, and comorbidities were common (hypertension 82.2%, coronary artery disease 42.8%, diabetes 33.6%). Over the study period, the incidence rate of fall-related major bleeding was 4.60 per 1000 person-years, and nearly all of these events (99.0%) resulted in traumatic intracranial hemorrhages. In unadjusted models, significant predictors for fall-related major bleeding included dementia (HR 1.84, 95%CI 1.31–2.58), fall within the past year (HR 1.60, 95%CI 1.11–2.29), depression (HR 1.48, 95%CI 1.21–1.80), hypertension (HR 1.24, 95%CI 1.00–1.54), abnormal renal/liver function (HR 1.50, 95%CI 1.06–2.11), prior stroke (HR 1.49, 95%CI 1.13–1.96), and labile international normalized ratio (INR) (HR 1.90, 95%CI 1.12–3.24). After adjusting for potential confounders, labile INR, dementia, depression, and stroke and remained significant predictors.

Conclusions: Fall-related major bleeding is a relatively uncommon event among older adults receiving anticoagulation for AF. However, several factors place patients at increased risk, and optimal management for this high-risk phenotype deserves further study.

708. Benefit-Risk of VKA for Atrial Fibrillation Before DOAC: A Cohort Study in a Claims and Hospitalization Database

Patrick Blin,[1,2] Caroline Dureau-Pournin,[1,2] Régis Lassalle,[1,2] Abdelilah Abouelfath,[1,2] Cécile Droz-Perroteau,[1,2] and Nicholas Moore,[1,3] *[1]INSERM CIC1401, Bordeaux, France; [2]ADERA, Pessac, France; [3]University of Bordeaux, Bordeaux, France.*

Background: Vitamin K antagonists (VKA) are a major iatrogenic cause of haemorrhage and hospital admissions, but the incidence of bleeding during VKA exposure for atrial fibrillation (AF), as well as ischemic event, is not well established in real life, and before introduction of direct oral anticoagulants (DOAC) for non-valvular AF (NVAF).

Objectives: The aim of this study was to assess real-life outcomes in new VKA users for AF.

Methods: Cohort study of new VKA users between 2007 and 2011, with a 2-year history and a 3-year follow-up censored at the end of 2012, was designed in the EGB, a 1/97 random sample of the French national healthcare claims and hospitalization database. AF population was defined as patients with full coverage for AF, hospitalization or probabilistic AF information in the database, and NVAF population as patients with AF diagnosis information (full coverage or hospitalization), without valvular disease history or other probable cause of VKA prescription. Outcomes were the first hospitalization for bleeding, arterial thrombotic event (ATE), acute coronary syndrome (ACS) and death. Incidence rate of outcomes was estimated during VKA exposure.

Results: Among 8894 patients identified, 3530 were classified in the AF population. Half were male (51.1%) with a mean age of 75.3 years, 87.3% had a CHA2DS2-VASc score ≥2 and 11.5% a HAS-BLED score >3. The incidence rate of bleeding was 29 patients (95%CI [24–34]) for 1000 PY exposed to VKA, including 6 [4–8] cerebral, 10 [7–13] digestive, and 14 [10–17] other bleeds. Incidence rates were 16 [12–19] for ACS, 14 [11–18] for ATE and 39 [33–45] deaths for 1000 PY exposed to VKA. Patient characteristics and incidence rates were very close for the 1813 patients with NVAF population criteria. For this last population, incidence rates were 29 [23–34] for bleeding, 15 [11–19] for ACS, 14 [10–18] for ATE, and 37 [31–43] deaths for 1000 PY exposed to VKA.

Conclusions: This study provides background reference for bleeding, ischemic events and deaths before the introduction of DOAC for NVAF with quite same frequency for AF and NVAF populations.

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709. Comparison of the Short-Term Bleeding Risk in Nonvalvular Atrial Fibrillation Patients Newly Treated with Dabigatran or Rivaroxaban Versus Vitamin K Antagonists: A French Nationwide Propensity-Matched Cohort Study

Géric Maura,[1] Pierre-Olivier Blotiere,[1] Kim Bouillon,[2] Cécile Billionnet,[1] Philippe Ricordeau,[1] François Alla,[1] Alain Weill,[1] and Mahmoud Zureik[2] *[1]Strategy and Research Department, National Health Insurance (CNAMTS), Paris, France; [2]Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Paris, France.*

Background: Bleeding risk has been observed to be significantly higher during the first 90 days of therapy in atrial fibrillation (AF) patients initiating warfarin. It remains unclear whether the non-vitamin K antagonists (VKA) oral anticoagulants (NOACs) are associated with a higher risk of bleeding during the early phase of anticoagulant therapy compared with VKA.

Objectives: The real-life bleeding risk of dabigatran or rivaroxaban was compared with VKA in anticoagulant-naive nonvalvular AF (nv-AF) patients.

Methods: Using data from the French medico-administrative databases (SNIIRAM-PMSI), this nationwide cohort study included patients with nv-AF who initiated dabigatran or rivaroxaban in July–November 2012 or VKA in July–November 2011. Patients presenting a contraindication to these agents were excluded. Dabigatran and rivaroxaban new users were matched to VKA new users using 1:2 matching on the propensity score. Patients were followed up for 90 days until hospitalized bleeding, death, loss to follow-up or 31 December of the inclusion year. In an intent-to-treat analysis, hazard ratios of major bleeding were estimated using Cox regression analyses for each NOAC type.

Results: All 8443 dabigatran-treated and 4651 rivaroxaban-treated patients were matched to 16 014 and 9301 VKA-treated patients, respectively. Dabigatran and rivaroxaban users had fewer comorbidities than VKA users, but the mean HAS-BLED score was comparable between NOAC and VKA users. Incidence rates of major bleeding were 32.7 and 37.1 per 1000 person-years in dabigatran-treated and VKA matched-treated patients and 36.5 and 35.6 per 1000 person-years in rivaroxaban-treated and VKA matched-treated patients, respectively. No .significant difference in bleeding risk was observed between dabigatran (HR = 0.88 [0.64–1.21]) or rivaroxaban (HR = 0.98 [0.64–1.51]) and VKA new users.

Conclusions: No difference was found between NOAC and VKA regarding the bleeding risk during the 90 days following treatment initiation in nv-AF patients. Physicians should exercise caution when initiating either NOAC or VKA.

710. Primary Non-adherence to Oral Anticoagulants in a Population-Based Cohort of New Users with Non-valvular Atrial Fibrillation in Spain

Clara L. Rodríguez-Bernal,[1,2] Gabriel Sanfélix-Gimeno,[1,2] Cristóbal Baixauli-Pérez,[1,2] and Salvador Peiró[1,2] *[1]Health Services Research, FISABIO-Salud Pública, Valencia, Spain; [2]Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Valencia, Spain.*

Background: New oral anticoagulants (NOAC) are expected to improve adherence as compared with vitamin K antagonists (VKA). Primary adherence is an important yet understudied component of adherence for oral anticoagulation (OAC) therapy.

Objectives: The aim of this study was to assess primary non-adherence (not filling the first prescription) to OAC and its associated factors in real-world clinical practice.

Methods: Population-based retrospective cohort including all patients with non-valvular atrial fibrillation newly prescribed OAC between November 2011 and February 2014 in the Valencia Region, Spain ($n = 21\,904$). Data were obtained by linking diverse electronic databases (including medical records and pharmacy claims) of the Valencia Health Department. Bivariate analysis and logistic multivariate models were carried out to assess the associations between primary non-adherence and several covariates adjusting by a propensity score (indication bias).

Results: The prevalence of primary non-adherence was 4.8% (VKA: 3.6%, NOAC: 10.4%, $p < 0.001$). In the multivariate analysis, patients with NOAC

showed higher odds of not filling their first prescription as compared with those prescribed VKA (OR: 3.17; 95%CI: 2.78–3.62). Other factors associated to primary non-adherence were being a foreigner (OR: 2.06 [1.54–2.74] for Europeans and 3.05 [1.33–6.98] for non-Europeans), dementia (OR: 1.76; 1.42–2.18), previous ischemic stroke (OR: 1.36; 1.08–1.71), visiting a cardiologist in the last year (OR: 1.51; 1.09–2.09) and copayment (OR: 1.37; 1.03–1.81). Older age (OR: 0.80; 0.69–0.93), emergency visits in the last year (OR: 0.80; 0.67–0.96), liver (OR: 0.74; 0.55–0.99) or renal (OR: 0.68; 0.52–0.89) disease and concomitant treatments (OR: 0.63 [0.53–0.74] for six to nine drugs and 0.56 [0.47–0.67] for ≥10 drugs) were associated with improved adherence.

Conclusions: Primary non-adherence among patients newly prescribed OAC was relatively low (4.8%) yet important owing to its potential clinical consequences. The type of anticoagulant prescribed was the strongest predictor of primary non-adherence.

711. Safety of New Anticoagulant Treatments in Swedish Patients with Non-valvular Atrial Fibrillation

Anastasia Nyman,[1] Julius J.K.M. Collin,[1] Natalia Borg,[1] and Marcus Gry[1] *[1]National Board of Health and Welfare, Stockholm, Sweden.*

Background: Concerns have been raised about the safety of the new oral anticoagulants (NOAC) in general practice settings.

Objectives: The aim of this study was to assess the risk of stroke, myocardial infarction, bleeding and mortality in NOAC compared with warfarin first-time users in patients with non-valvular atrial fibrillation.

Methods: Design: National population-based registers in Sweden were used to identify a cohort of first-time NOAC users with a diagnosis of non-valvular atrial fibrillation between January 2012 and November 2013. Follow-up was until time to event, censoring or end of follow-up (30 November 2014). Setting: The study comprised 1932 dabigatran, 775 rivaroxaban, 187 apixaban and 18 221 warfarin users. Exposures: First-time use of dabigatran, rivaroxaban, apixaban and warfarin. Main outcome measures: primary outcome, stroke. Secondary outcomes: myocardial infarction, major, gastrointestinal and intracranial bleedings, and mortality. Statistical analysis: We used propensity scores to reduce confounding and Cox proportional hazards regression.

Results: We found a 74% (95%CI 1.09–2.65) excess risk for gastrointestinal bleedings in dabigatran users compared with warfarin users. The risk was even more pronounced in elderly (>75) or patients using more than five other drugs simultaneously. There was a 62% (95%CI 1.16–2.20) excess risk for major bleedings in rivaroxaban users compared with warfarin. The risk was more pronounced in elderly, or patients using less than five other drugs or patients not having used other anticoagulant treatment for more than 2 years ago. A risk of 3.66 (95%CI 1.25–8.59) for intracranial bleeding was noted in patients who have used other anticoagulant treatment less than 2 years before their first-time use of Rivaroxaban. No risks were seen for apixaban, probably owing to small numbers.

Conclusions: In general practice settings, dabigatran, rivaroxaban and apixaban were not associated with risk of stroke, myocardial infarction and death. However, age, simultaneous use of other drugs or other anticoagulant use before current drug treatment suggest that these are important factors contributing to the excess risk of bleedings in dabigatran and rivaroxaban users.

712. Characteristics of Patients Initiating Oral Anticoagulants in Routine Care

Chandrasekar Gopalakrishnan,[1] Krista F. Huybrechts,[1] Dalia Shash,[2] Kristina Zint,[2] John D. Seeger,[1] Dorothee B. Bartels,[2] Joan Landon,[1] Katsiaryna Bykov,[1] and Sebastian Schneeweiss[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Corporate Department of Global Epidemiology, Boehringer Ingelheim GmbH, Ingelheim, Germany.*

Background: Dabigatran etexilate is a new oral anticoagulant developed as an alternative to vitamin K antagonists. Factors related to the expected effectiveness and safety of dabigatran may lead to selective prescribing patterns, in particular in the early post-marketing phase.

Objectives: We sought to describe key differences in the characteristics of patients initiating dabigatran versus warfarin.

Methods: Within a large US commercial health insurance database (MarketScan), we compared baseline characteristics of patients ≥18 years with nonvalvular atrial fibrillation at risk for stroke who newly initiate dabigatran or warfarin between October 2010 and December 2012. All characteristics were assessed in the 12 months prior to treatment initiation and were identified from medical and prescription claims and enrollment files. Time trends during the study period were evaluated in 6-month intervals.

Results: We identified 18 560 new dabigatran users and 41 103 new warfarin users during the study period. Dabigatran initiators were younger (mean age: 67.1 vs. 70.5 years) and healthier overall than warfarin initiators. They had lower mean CHA2DS2-VASC scores (2.87 vs. 3.44), an indicator of stroke risk and lower mean HAS-BLED scores (2.14 vs. 2.39), an indicator of bleeding risk, compared with warfarin initiators. Dabigatran initiators had a lower burden of comorbidities, including, for example, renal dysfunction (9.0% vs. 16.7%), congestive heart failure (16.3% vs. 22.0%), coronary artery disease (28.7% vs. 32.9%) and prior stroke (7.9% vs. 10.0%), compared with warfarin initiators. They were also less likely to have been hospitalized in the 30 days prior to treatment initiation and in general had less intense healthcare use. The aforementioned differences in characteristics were consistently observed over the entire study period and became slightly more pronounced in later time periods. These patterns were also observed in another US insurance claims database (Optum Clinformatics).

Conclusions: In the early post-marketing period, patients initiating dabigatran were younger and healthier than warfarin initiators. Such differences need to be carefully accounted for in comparative effectiveness or safety studies.

713. Applying the Test-Negative Design to Vaccine Safety Studies: Risk of Narcolepsy Associated with A/H1N1 (2009) Pandemic Influenza Vaccination in Quebec

Catherine Cohet,[1] Jacques Montplaisir,[2,3] Dominique Petit,[2] Marie-Josée Quinn,[2] Manale Ouakki,[4] Geneviève Deceuninck,[5] Alex Desautels,[2,6] Emmanuel Mignot,[7] Vincent Bauchau,[8] Vivek Shinde,[1] and Philippe De Wals[9] *[1]Global Epidemiology, GlaxoSmithKline Vaccines, Wavre, Belgium; [2]Centre for Advanced Research in Sleep Medicine, Hôpital du Sacré-Coeur, Montreal, QC, Canada; [3]-Department of Psychiatry, University of Montreal, Montreal, QC, Canada; [4]Quebec National Public Health Institute, Québec City, QC, Canada; [5]Quebec University Hospital Research Center, Quebec City, QC, Canada; [6]Department of Medicine, University of Montreal, Montreal, QC, Canada; [7]Stanford Center for Sleep Sciences and Medicine, Stanford University of Medicine, Palo Alto, CA, USA; [8]Vaccine Safety Research Group, GlaxoSmithKline Vaccines, Wavre, Belgium; [9]Department of Social and Preventive Medicine, Laval University, Quebec City, QC, Canada.*

Background: The test-negative design has been extensively used for influenza vaccine effectiveness studies to minimize confounding by healthcare seeking behavior but has not been used for evaluating adverse events. An increased risk of narcolepsy with GlaxoSmithKline's inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine was reported in Europe. A cohort study in Quebec showed a small cluster of narcolepsy cases in vaccinated individuals

Objectives: Post-authorisation safety study was performed to assess the risk of narcolepsy following GSK's A/H1N1pdm09 vaccine in Quebec using an alternate design

Methods: We conducted a test-negative case–control analysis nested in a 2-year population-based cohort study. Suspected and confirmed narcolepsy cases with onset of excessive daytime sleepiness from 1 January 2009 to 31 December 2010 were referred by neurologists and lung specialists to a reference sleep center for standardized re-evaluation and case confirmation using Brighton criteria. Controls were defined as patients consulting for sleep-related symptoms without cataplexy and 'testing negative' for sleep tests. Immunization status was obtained from the provincial H1N1 immunization registry. Odds ratios (ORs) were computed using conditional logistic regression

Results: The analyses included all 24 cases from the cohort and 42 controls. The unadjusted OR was 0.71 [95% confidence interval (CI): 0.14–3.59]. In adjusted

models, ORs ranged from 0.7 to 1.4 with 95%CI including 1.0. Significant differences between cases and controls on HLA prevalence and sleep tests, and re-evaluation of controls after 1 year, confirmed the validity of diagnoses in cases and controls. These estimates excluded the range of risks observed in the cohort analysis.

Conclusions: The test-negative design in vaccine safety studies of complex outcomes such as neurological/immune-mediated diseases might mitigate selection and referral biases on the assumption that cases and controls drawn from the same population are comparable on confounders such as propensity to seek care and likelihood to be diagnosed.

714. Risk of Anaphylaxis Following Influenza Vaccination: Results from the Vaccine Safety Datalink

Frank DeStefano,[1] Eric Weintraub,[1] Jonathan Duffy,[1] Lakshmi Sukumaran,[1] Steven J. Jacobsen,[2] Nicola P. Klein,[3] Simon J. Hambidge,[4] Grace M. Lee,[5] Lisa A. Jackson,[6] Stephanie A. Irving,[7] Jennifer P. King,[8] Elyse O. Kharbanda,[9] Robert A. Bednarczyk,[10] and Michael M. McNeil.[1] *[1]CDC, Atlanta, GA, USA; [2]Southern California Kaiser Permanente, Pasadena, CA, USA; [3]Kaiser Permanente Vaccine Study Center, Oakland, CA, USA; [4]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA; [5]Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston, MA, USA; [6]Group Health Research Institute, Seattle, WA, USA; [7]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA; [8]Marshfield Clinic Research Foundation, Marshfield, WI, USA; [9]HealthPartners Institute for Education and Research, Minneapolis, MN, USA; [10]School of Public Health, Emory University, Atlanta, GA, USA.*

Background: In the USA, everyone 6 months of age or older is recommended to receive influenza vaccine, and more than 100 million doses are administered annually. Anaphylaxis is the one life-threatening medical emergency that is known to occur after influenza vaccination, but the risk has not been quantified.

Objectives: The aim of this study was to determine the risk of anaphylaxis following influenza vaccination.

Methods: Using immunization and medical care data from the Vaccine Safety Datalink, we determined rates of anaphylaxis following vaccinations in children and adults. We first identified all patients with a vaccination record from nine large integrated healthcare systems during January 2009 to December 2011. We used a computerized algorithm based on ICD9 diagnostic codes and epinephrine prescriptions to identify potential cases of anaphylaxis. Clinical charts were reviewed, and Brighton Collaboration criteria were applied to confirm anaphylaxis case status. We used data on doses administered as the denominator for calculating incidence rates and confidence intervals (CIs).

Results: We identified 17 anaphylaxis cases following 11 million influenza vaccine doses administered alone or with other vaccines; 14 cases occurred after trivalent inactivated influenza vaccine (TIV) and three after 2009 pandemic monovalent inactivated influenza vaccine (MIV). No cases followed a live attenuated influenza vaccine (>800 000 doses). Influenza vaccinations given alone without other concomitant vaccines provided the most reliable vaccine-specific rates: 1.35 (95%CI, 0.65–2.47) per million doses for TIV (10 cases; 7 434 628 doses given alone) and 1.83 (95%CI, 0.22–6.63) per million doses for MIV (two cases; 1 090 279 doses given alone).

Conclusions: In a large population-based study, we found that the risk of anaphylaxis following inactivated influenza vaccines is one to two per million doses. Despite its rarity, anaphylaxis is a potentially life-threatening medical emergency that vaccine providers need to be prepared to treat.

715. Heterogeneity of Rotavirus Vaccine Efficacy Among Infants in Developing Countries

Joann F. Gruber,[1,2] Darcy A. Hille,[2] G. Frank Liu,[2] Susan S. Kaplan,[2] Micki Nelson,[2] Michelle G. Goveia,[2] and T. Christopher Mast[2] *[1]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA; [2]Merck & Company, Inc, Whitehouse Station, NJ, USA.*

Background: Prior to vaccine introduction, rotavirus was the leading cause of severe diarrhea worldwide in children under 5. Although efficacy of rotavirus vaccines has been high in developed countries, efficacy has been lower in developing countries where most rotavirus-associated deaths occur.

Objectives: The aim of this study was to determine if there is heterogeneity of rotavirus vaccine efficacy by infant characteristics in developing countries.

Methods: We conducted a post-hoc analysis of data from a randomized, placebo controlled trial of pentavalent rotavirus vaccine conducted from 2007 to 2009 in Ghana, Kenya, Mali, Bangladesh, and Vietnam. Infants enrolled at 4–12 weeks of age ($N=7504$) received either three doses of vaccine/placebo and were followed up for 2 years. Active surveillance identified cases of rotavirus gastroenteritis occurring 14 days after the final dose. Infant characteristics were collected at the first study visit. We calculated vaccine efficacy ((1 − rate ratio) * 100%) and 95% confidence interval (CI) against severe rotavirus gastroenteritis (Vesikari score ≥ 11) using Poisson regression. We assessed heterogeneity of efficacy by age at vaccination, gender, HIV status, breastfeeding status, and nutrition status. Heterogeneity was considered to be present when the p-value for interaction term between the factor and vaccine status was lower than $\alpha=0.1$. All analyses were stratified by region and country

Results: Children receiving first vaccine dose at <8 weeks had lower efficacy (23.7%; 95%CI −8.2, 46.3) than those vaccinated at ≥8 weeks (59.1%; 95% CI 34.0, 74.6) in African countries. In Ghana, male children had lower efficacy (35.1%; 95%CI −15.8, 63.6) as compared with female children (75.9%; 95% CI 44.9, 89.5), and underweight children had lower efficacy (19.0%; 95%CI −75.1, 62.5) as compared with those not underweight (67.9%; 95%CI 41.3, 82.4). Female children in Asia had lower efficacy (6.2%; 95% CI −143.3, 63.8) than male children (65.2%; 95%CI 30.3, 82.6) for 1 year of follow-up.

Conclusions: There was heterogeneity of vaccine efficacy across risk factors and region. We saw heterogeneity of efficacy across age at vaccination, gender, and underweight status in Africa whereas only for gender in Asia.

716. Effectiveness of Zostavax™ in Preventing Herpes Zoster in a U.S. Managed Care Organization

Roger Baxter,[1] Bruce Fireman,[1] Joan Bartlett,[1] Morgan Marks,[2] John Hansen,[1] Edwin Lewis,[1] Laurie Aukes,[1] Yong Chen,[2] and Patricia Saddier[2] *[1]Kaiser Permanente Vaccine Study Center, Oakland, CA, USA; [2]Pharmacoepidemiology Department, Merck Sharp & Dohme, Corp., North Wales, PA, USA.*

Background: Zostavax™, a single-dose live zoster vaccine, is licensed in >50 countries for the prevention of herpes zoster (HZ) and postherpetic neuralgia (PHN), its main long-lasting pain complication. Duration of protection is being assessed through a long-term observational study.

Objectives: The aim of this study was to present preliminary results on the vaccine effectiveness (VE) in preventing HZ during the first 7 years of routine use.

Methods: The study is conducted at Kaiser Permanente Northern California (KPNC). KPNC began using zoster vaccine in individuals ≥60 years old (60+) in 2006 and in ≥50 year olds (yo) in 2011. KPNC members are included in the study when they become age eligible for the vaccine. Incident HZ is defined as a new HZ episode without evidence of HZ in the prior year. This preliminary analysis included HZ cases identified by having a diagnosis code of HZ with an antiviral prescription or a positive viral test. VE by time since vaccination was estimated using Cox proportional hazard models stratified by age at vaccination and adjusted for sex, age, race/ethnicity, calendar time, and several time-varying variables, including healthcare use, comorbid conditions, and immune-compromise status.

Results: From January 2007 to December 2013, a total of ~1.3 million study individuals ≥50 yo contributed ~4.9 million person-years of follow-up. In 2013, vaccine coverage was >40% in 60+ yo but only 4% in 50–59 yo. In all age groups (50–59, 60–69, 70–79, and 80+ yo at the time of vaccination), VE in preventing HZ was >60% during the first year following vaccination (70%, 73%, 65%, and 64%, respectively), decreased in the second year, and tended to remain stable afterwards in 60+. The average VE over the first 7 years was 51%, 45%, and 46% in people vaccinated at ages 60–69, 70–79, and 80+ yo, respectively.

Conclusions: This study suggests that the average VE of a single dose of Zostavax™ in routine use was ~40–50% over the 7 years following vaccination in people vaccinated when 60+. In 50–59 yo, VE was 70% at year 1. These results were consistent with published clinical trial results. The study will continue to further assess the duration of protection conferred by this vaccine against both HZ and PHN.

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717. Risk of Autoimmune Diseases (AD) After Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine Immunization in Women Aged 9 to 25 Years in the United Kingdom: An Observational Cohort Study

Corinne Willame,[1] Dominique Rosillon,[2] Julia Zima,[2] Maria-Genalin Angelo,[2] Anke Stuurman,[3] Hilde Vroling,[3] Tjeerd van Staa,[4] Rachael Boggon,[5] Eveline Bunge,[3] Manel Pladevall-Vila,[6] and Laurence Baril[2]
[1]Business & Decision Life Sciences on Behalf of GSK Vaccines, Wavre, Belgium; [2]GSK Vaccines, Wavre, Belgium; [3]Pallas Health Research and Consultancy, Rotterdam, The Netherlands; [4]Health eResearch Centre, Farr Institute of Health Informatics Research, University of Manchester (At the Time of Study: CPRD Research Group, London, UK), Manchester, UK; [5]CPRD Research Group, London, UK; [6]RTI Health Solutions, Barcelona, Spain.

Background: The HPV-16/18 AS04-adjuvanted vaccine is indicated for protection against cervical cancer. The risk of AD after vaccination needs to be evaluated.

Objectives: The aim of this study was to assess the risk of AD (two co-primary endpoints: neuroinflammatory/ophthalmic and other) in women aged 9–25 years within 1 year after the first dose of HPV-16/18 vaccine.

Methods: Four cohorts (65 000 subjects each) were defined in the UK Clinical Practice Research Datalink General Practice OnLine Database: one exposed female cohort (≥1 vaccine dose September 2008 to August 2010) and three unexposed cohorts—one concurrent male cohort (September 2008 to August 2010), one historical male cohort and one historical female cohort (September 2005 to August 2007) (NCT01953822). AD risk was compared between cohorts (with the historical cohort as reference group) by Poisson regression. Sensitivity analysis considered confirmed and non-confirmed cases.

Results: In all cohorts, 155 subjects had AD first symptom within 1-year follow-up; 109 were confirmed AD. The main analysis based on confirmed cases showed no increased risk of neuroinflammatory/ophthalmic AD: no confirmed cases in female cohorts and incidence rate ratios (IRR) (95%CI) = 0.95 (0.06–15.18) in male cohorts; for other AD: IRR = 1.41 (0.86–2.31) in female and IRR = 1.77 (0.94–3.35) in male cohorts. Disease-specific risks were evaluated for three diseases with ≥10 cases in both female cohorts: Crohn's disease (IRR = 1.21 [0.37–3.95] and IRR = 4.22 [0.47–38.02] for female and male cohorts, respectively), autoimmune thyroiditis (IRR = 3.75 [1.25–11.31] for female and no confirmed cases for male cohorts) and type 1 diabetes mellitus (IRR = 0.30 [0.11–0.83] for female [risk adjusted for male cohort effect] and IRR = 2.46 [1.08–5.60] for male cohorts). Sensitivity analysis confirmed main analyses except for autoimmune thyroiditis in female cohorts, IRR = 1.45 (0.79–2.64).

Conclusions: There was no evidence of an increased risk of AD in women aged 9–25 years after HPV-16/18 vaccination. After disease-specific analysis, the risk of autoimmune thyroiditis was increased, and the risk of type 1 diabetes was decreased in vaccinated women.

Funding: GlaxoSmithKline Biologicals SA

718. Using Robust Methods to Assess the Risk of Serious Adverse Events Following Quadrivalent HPV Vaccination

Linda E. Levesque,[1] Leah M. Smith,[1] Erin Liu,[1] Melanie Cheung,[1] W.T. Lim,[1] Diane Lougheed[1], Anne Ellis[1], Kim Sears[1], Heather Whitaker[2], and C. P. Farrington[2]
[1]Queen's University, Kingston, ON, Canada; [2]Mathematics and Statistics, The Open University, Milton Keynes, UK.

Background: To date, post-licensure evaluations of serious adverse events following quadrivalent HPV (qHPV) vaccination have compared vaccinated and unvaccinated girls, an approach prone to confounding. The self-controlled case series (SCCS) is a case-only, self-matched method that inherently controls for time-invariant confounding.

Objectives: The aim of this study was to assess the risk of autoimmune disorders, serious respiratory-related events, and seizures and convulsions following qHPV vaccination using the SCCS.

Methods: We identified a cohort of girls eligible for Ontario's publicly funded, school-based grade 8 qHPV vaccination program in 2007–2013 using the universal health insurance and immunization databases of Ontario, Canada. Girls were followed up from September 1 of grade 8 until 31 March 2014 (study end). Only vaccinated cases were considered for the SCCS analysis. Follow-up time was classified as 'exposed' during prespecified exposure risk periods following each dose and as 'unexposed' otherwise. The study had >90%

power to detect a doubling in the risk of the endpoints. We estimated rate ratios (RR) and 95% confidence intervals (CIs) using conditional Poisson regression adjusted for four time-variant factors: age, season, concurrent vaccinations and concurrent infections.

Results: The cohort consisted of 290 793 girls with a mean age of 13.2 years at cohort entry; girls were followed up for an average of 2.9 years. We identified 681, 1139 and 481 vaccinated cases of autoimmune disorders, incident asthma and seizures, respectively. Of these, 11.3% (autoimmune disorders), 0.9% (asthma) and 17.9% (seizures) were classified as exposed. The adjusted RR was 1.20 (95%CI 0.85–1.47) for autoimmune disorders, 0.91 (0.26–1.34) for asthma and 1.22 (0.94–1.57) for seizures. Risk estimates were independent of a history of predisposing risk factors.

Conclusions: We did not identify an increased risk of autoimmune disorders, serious respiratory-related events or seizures/convulsions following qHPV vaccination. The results of this large, robust study address public concerns about the safety of the qHPV vaccine in this young age group.

719. The Effectiveness of Corticosteroid Treatment on Septic Shock Patient Outcomes in Intensive Care Units

Christine A. Motzkus-Feagans,[1] HuiFang Zhao,[1] Sybil Crawford[2], and Craig Lilly[3] *[1]Clinical and Population Health Research Program, University of Massachusetts Medical School, Worcester, MA, USA; [2]Division of Preventive and Behavioral Medicine, University of Massachusetts Medical School, Worcester, MA, USA; [3]Departments of Medicine, Anesthesiology, and Surgery, University of Massachusetts Medical School, Worcester, MA, USA.*

Background: Septic shock is the most common cause of death in intensive care units (ICUs) with mortality rates of up to 60%. Corticosteroid insufficiency occurs in up to 60% of critically ill patients, inclusive of septic shock. Current research on steroid therapy is not always applicable to diverse ICU populations.

Objectives: The aim of this study was to evaluate the role of steroid treatment on outcomes of patients with septic shock.

Methods: A prospective cohort study of adult patients with septic shock admitted to seven ICUs at an academic medical center from October 2007 to December 2009 was designed. Patients with conditions requiring long-term corticosteroid treatment were excluded. All data were extracted from electronic medical records. Steroid treatment was defined from receipt of the first dose of intravenous hydrocortisone. The primary outcome was hospital mortality. Septic shock was defined as a diagnosis in the electronic medical record at admission or during an ICU stay; onset time was considered time at first dose of a vasopressor. Propensity scores were calculated for each patient's probability of receiving steroid therapy. Multivariate logistic regression was used to evaluate the primary endpoint.

Results: A total of 13 199 patients were admitted to ICUs during the study. A total of 841 septic shock patients were included; 290 patients (34%) received steroid therapy. Steroid-treated patients were 1.67 times more likely to die in hospital than non-steroid-treated patients (95%CI 1.26–2.23). After propensity score matching, steroid treated patients were 1.44 times more likely to die in hospital than non-steroid-treated patients (95%CI 1.01–2.08). After controlling for all other confounders and adjusting for propensity scores, steroid treated patients were 1.51 times more likely to die in hospital (95%CI 1.04–2.20).

Conclusions: This study found that steroid-treated patients were more likely to die in hospital compared with non-steroid-treated patients. This finding contrasts clinical practice recommending steroid therapy and the 2008 Surviving Sepsis Campaign; however, this population differs from populations in randomized controlled trials. Study strengths include use of propensity scores and a diverse ICU population.

720. Addition of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Risk of Acute Kidney Injury (AKI) in Hospitalized Patients Receiving Vancomycin

Nakyung Jeon[1] and Almut G. Winterstein[1,2] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA; [2]Department of Epidemiology, University of Florida, Gainesville, FL, USA.*

Background: Risk and risk factors for vancomycin-induced acute kidney injury (AKI) are well described. However, evidence on the contribution of nonsteroidal anti-inflammatory drugs (NSAIDs) to this risk is missing.

Objectives: This study aims to examine the risk of AKI associated with NSAIDs exposure when added to a vancomycin regimen in hospitalized patients.

Methods: We conducted a retrospective cohort study of patients admitted to two University of Florida affiliated hospitals between January 2012 and October 2013. Patients aged 18 or more who received vancomycin for 2 to 28 days were identified using the hospitals' electronic health records. Patients were followed up within a time-dependent Cox proportional hazards model up to 5 days after vancomycin discontinuation or hospital discharge. NSAID exposure was alternatively defined as ever use, the cumulative number of days (1, 2–3, and >3 days), daily dose (high/low), and NSAID types (high/low AKI risk) among vancomycin users. The days before NSAID initiation were assigned to no-use time. All models were adjusted for a propensity score that summarized potential confounders measured during 48 hours before cohort entry and the number of vancomycin days as time-dependent covariate.

Results: Our cohort included 9249 patients with 2105 (12 563 person-days) exposed and 7144 (53 012 person-days) not exposed to NSAIDs during vancomycin therapy. During the mean follow-up time of 6.3 ± 4.5 days, 1356 AKI occurred, including 283 during NSAIDs use. The ever use of NSAIDs on vancomycin was not associated with an increased risk of stage 1 AKI (HRa: 0.98 [0.93–1.03]) but showed significance for stage 2 AKI (HRa: 1.58 [1.19–2.11]). Associations with stage 1 AKI became significant for all alternative exposure definitions including cumulative, high-dose, and high-risk NSAID (indomethacin, naproxen, and ketorolac) use with adjusted HR of 1.58 [1.19–2.11], 1.30 [1.01–1.67] and 1.31 [1.00–1.73], respectively.

Conclusions: NSAIDs use during vancomycin therapy may increase the risk for AKI when used prolonged or in high dose. High-risk nephrotoxic NSAIDs, mostly driven by ketorolac, were independently associated with the risk of AKI.

721. Increased Anti-infective Treatments Preceding a Diagnosis of Primary Immune Thrombocytopenia

Charlotta Ekstrand,[1] Marie Linder,[1] Honar Cherif,[2] Helle Kieler,[1], and Shahram Bahmanyar[1] *[1]Center for Pharmacoepidemiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [2]Department of Medical Sciences, Haematology, Uppsala University, Uppsala, Sweden.*

Background: An important complication after diagnosis of primary chronic immune thrombocytopenia (cITP) is infections, which have mostly been connected to the immunomodulation treatment. However, infections may trigger autoimmune diseases and may be a complication of an already defective immune system.

Objectives: The aim of this study was to investigate anti-infective treatments before cITP diagnosis, exclusively those dispensed within 1 year before cITP onset.

Methods: We identified 1087 adults (18 years or older) with a diagnosis of primary cITP between 2006 and 2012 using the Swedish Patient Register. Codes D69.3 and D69.4 from the Tenth Revision of the International Classification of Diseases were used to identify patients. Data on treatments for infections not already listed as cause of secondary ITP were retrieved from the Prescribed Drug Register. The standardized incidence ratios (SIR; the ratio of the observed to the expected number of anti-infective prescriptions dispensed) and 95% confidence intervals (CIs) were estimated as a measure of relative risk of anti-infective treatment for the year preceding cITP diagnosis. The expected numbers of anti-infective treatment was calculated using the rates from the general population, divided into strata of sex, age (in 5-year groups), and year of diagnosis.

Results: Patients with cITP were exposed to anti-infective treatments before diagnosis more often that the general population, SIR = 1.37, 95%CI (1.25–1.5). There was no notable risk difference between men and women. Analysis stratified for age groups (in 5-year intervals) showed increased risks for almost all age groups until the age 65 years and then moved towards null. Higher magnitude SIRs observed included the following: 1.69 (1.24–2.24) for macrolides, lincosamides and streptogramins, 1.54 (1.00–2.28) for direct acting antivirals and 1.31 (1.05–1.61) for tetracyclines.

Conclusions: Patients with cITP have increased overall risk of anti-infective treatments before the diagnosis, with more marked risk for antibacterial treatments. The findings indicate that infection is

related not only to the immunomodulation treatment but also to the disease itself.

722. The Risk of Tendon Rupture in Association with Use of Oral or Inhaled Glucocorticoids

Julia Spoendlin,[1,2] Christian Meier,[3], Susan S. Jick,[4] and Christoph R. Meier[1,2,4] *[1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [2]Hospital Pharmacy, University Hospital Basel, Basel, Switzerland; [3]Division of Endocrinology, Diabetes and Metabolism, University Hospital Basel, Basel, Switzerland; [4]Boston Collaborative Drug Surveillance Program, Boston University, School of Public Health, Lexington, USA.*

Background: Glucocorticoid (GC)-induced tendon ruptures have been reported over decades. Tendinotoxic effects of GC were shown *in?vitro* and *in?vivo*, but evidence to quantify this effect in clinical practice remains scarce.

Objectives: The aim of this study was to quantify the association between incident GC use (oral and inhaled separately) and incident Achilles or biceps tendon rupture (ATR/BTR).

Methods: For a matched (1:4) case–control analysis using the UK-based Clinical Practice Research Datalink, we identified case patients aged 18 to 90 years with an incident diagnosis of ATR or BTR between 1995 and 2013. Incident exposure to oral GC was stratified by indication (e.g. respiratory disease, connective tissue disease), by timing (last prescription $</\geq$180 days), and by duration of therapy (time since therapy start, substratified into continuous or intermittent use). Continuous prednisone-only users were stratified by average daily dose. Incident current inhaled GC use was stratified by timing and duration (number of recorded prescriptions) of therapy.

Results: Among 8202 cases (61.3% ATR and 38.7% BTR), we observed an OR of 2.07 (95%CI 1.80–2.39) in incident current oral GC users. Odds ratios were highest ($>$3.0, statistically significant) in continuous GC users with therapy duration of $<$1 month to 1.5 years (slightly lower ORs around 2.0 thereafter) and waned off shortly after therapy stop. This pattern was similar in patients with a respiratory disease and in those with underlying connective tissue disease and was seen in ATR and BTR patients separately. Relative risk estimates correlated with the average daily prednisone dose (highest OR 3.71, 95%CI 2.00–7.03, $\geq$10 mg/day). Use of inhaled GCs revealed ORs around unity across all strata of timing and duration of use.

Conclusions: Our results provide evidence of a more than twofold increased relative risk of ATR/BTR during oral GC therapy, irrespective of the underlying indication. The relative risk estimate closely correlated with the timing of therapy start and stop and increased with increasing daily dose. This risk pattern is similar to the one reported for GC-induced fractures. Inhaled GC use did not affect the relative risk estimate for ATR/BTR.

723. The Effect on Total Mortality of Adding Inhaled Corticosteroids to Long-Acting Bronchodilators for COPD: A Focus on Patients with Frequent Exacerbations

Mirko Di Martino,[1] Nera Agabiti,[1] Silvia Cascini,[1] Ursula Kirchmayer,[1] Valeria Belleudi,[1] Danilo Fusco,[1] Luigi Pinnarelli[1], Lisa Bauleo[1], Claudio Voci[2], Elisabetta Patorno[3], Riccardo Pistelli[4], and Marina Davoli[5] *[1]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [2]Management Control Unit, Modena University Hospital, Modena, Italy; [3]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [4]Department of Respiratory Physiology, Catholic University, Rome, Italy; [5]Department of Epidemiology, on Behalf of the OUTPUL Study Group; Lazio Regional Health Service, Rome, Italy.*

Background: Chronic therapy with long-acting bronchodilators (LB) is recommended to treat moderate to severe chronic obstructive pulmonary disease (COPD). Although the benefits of adding inhaled corticosteroid (ICS) to LB are still unclear, frequent exacerbators (FEs) are suggested to add ICS to their LB treatment.

Objectives: The objectives of this study are to analyze whether adding ICS to LB therapy reduces mortality and to perform an in-depth analysis on FEs.

Methods: We enrolled patients discharged from hospital with COPD diagnosis between 2006 and 2009 in the Lazio region, Italy. FE phenotype was defined as presence of previous COPD hospitalizations or concomitant use of oral corticosteroids and antibacterials in the 12 months before enrollment. Only new users of LB or ICS following enrollment were included. A 4-day

time window was used to classify patients into "LB alone" or "LB plus ICS" initiators. We used propensity score to balance the study groups. Patients were censored at the time of discontinuation of the initial drug, death, end of 1-year follow-up, or end of the study period (December 2010), whichever came first. Adjusted hazard ratios (HR) were estimated by Cox regression.

Results: Among the 18 618 adults enrolled, 12 210 initiated "LB plus ICS" therapy and 6408 "LB alone". Crude mortality rates were 110 and 143 cases per 1000 person-years in the "LB plus ICS" and "LB alone" groups, respectively. The HR was 0.84 (95% CI: 0.72–0.98; *p*-value: 0.027). A total of 2256 FEs were analyzed; 1505 initiated "LB plus ICS" whereas 751 "LB only". When analyzing FEs, the benefit of the combination therapy was more pronounced, HR = 0.63 (95%CI: 0.44–0.90; *p*-value: 0.012).

Conclusions: Our findings showed a beneficial effect on mortality of adding ICS to LB. The advantage was much more pronounced in FEs. Recently, the FE phenotype has been hypothesized to be associated with persistent systemic inflammation. The higher effect of the combined treatment in FEs suggests a crucial role of inflammatory mechanisms and the potential benefit of anti-inflammatory inhaled drugs.

724. Preadmission Use of Glucocorticoids and Short-term Mortality After Stroke: A Nationwide Population-Based Cohort Study

Jens Sundbøll,[1,2] Morten Schmidt,[1,2] Erzsébet Horváth-Puhó,[1] Olaf M. Dekkers,[3,4] Christian F. Christiansen,[1] Lars Pedersen,[1] Jan P. Vandenbroucke,[3] Hans Erik Bøtker,[2] and Henrik T. Sørensen[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands; [4]Department of Clinical Endocrinology and Metabolism, Leiden University Medical Centre, Leiden, The Netherlands.*

Background: The prognostic impact of glucocorticoids on stroke mortality remains unclear.

Objectives: The aim of this study was to examine whether preadmission use of glucocorticoids is associated with short-term mortality following ischemic stroke, intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH).

Methods: We conducted a nationwide population-based cohort study using medical registries in Denmark. We identified all patients with a first-time inpatient diagnosis of stroke between 2004 and 2012. We defined glucocorticoid use as current use (most recent prescription redemption <90 days before admission), former use (most recent prescription between 90 and 180 days before admission), and non-use (no prescription within 180 days before admission). Current use was further classified as new (first-ever prescription <90 days before admission) or long-term use (first-ever prescription >90 days before admission). We used Cox regression to estimate hazard ratios as a measure of 30-day mortality rate ratios (MRRs) with 95% confidence intervals (CIs), controlling for potential confounders.

Results: We identified 100 042 patients with a first-time stroke. Of these, 83 735 patients had ischemic stroke, 11 779 had ICH, and 4528 had SAH. Absolute mortality risk was higher for current users compared with non-users for ischemic stroke (19.5% vs. 10.2%), ICH (46.5% vs. 34.4%), and SAH (35.0% vs. 23.2%). For ischemic stroke, the adjusted 30-day MRR was increased among current users compared with non-users (1.58, 95%CI: 1.46–1.71), driven by the effect among new users (1.80, 95%CI: 1.62–1.99). Current users had a more modest increase in adjusted 30-day MRR for hemorrhagic stroke (1.26, 95%CI: 1.09–1.45 for ICH and 1.40, 95%CI: 1.01–1.93 for SAH) compared with non-users. Apart from a small effect on ischemic stroke (1.17, 95% CI: 1.01–1.36), former use was not associated with mortality.

Conclusions: Preadmission use of glucocorticoids was associated with increased 30-day mortality among patients with ischemic stroke, ICH, and SAH.

725. The New FDA Pregnancy Label—And How to Fill It (Sponsored by the Medications in Pregnancy Special Interest Group)

Carol Louik,[1] Leyla Sahin,[2] Sara Ephross,[3] Lyn Colvin,[4] and William Cooper[5] *[1]Slone Epidemiology Center, Boston University, Boston, MA, USA; [2]Division of Pediatric and Maternal Health, Food and Drug Administration, Silver Spring, MD, USA; [3]Worldwide Epidemiology, GlaxoSmithKline, Research Triangle Park, NC, USA; [4]Telethon Kids Institute, Subiaco, Western Australia, Australia; [5]Vanderbilt University, Nashville, TN, USA.*

Background: In December 2014, the US FDA issued the "Pregnancy and Lactation Rule" (PLLR) to define the content and format of labeling of prescription medications. Previously, prescription medications were classified into one of five categories designated as A, B, C, D, and X. The PLLR requires removal of these categories and inclusion instead of "a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation". As pregnant women are usually excluded from clinical trials during drug development, epidemiological data collected in the post-approval setting are the main source of information regarding the safe use of a drug in pregnancy.

Objectives: This symposium will help attendees better understand the details of this new regulation, the kinds of information that will be needed to appropriately modify current labeling, and from what sources this information can be obtained.

Description: In this symposium, we will present details of the new FDA rule and will describe specifically what products it will affect, when the new labeling will be required, and what types of information will be needed to meet the new requirements. We will also discuss the implications for industry including how the new labeling requirements inform the need for a systematic approach to evaluating and interpreting medication and pregnancy information. Although this new regulation is specific to the US drug industry, we will review current labeling requirements in the European Medicines Agency and Australia and discuss whether similar changes may be expected there. We will also describe sources for obtaining the data that will be required to fulfill the new regulation. These will include the full spectrum of epidemiological data including, but not limited to, large electronic databases and ongoing cohort and case–control surveillance systems.

726. Exploring Innovative Methods to Identify Patient Subgroup Treatment Response

John Rigg[1], Matthew Hankins[1], Andrew Roddam[2], Jerry Avorn[3], Joseph Kim[4]. *[1]Real World Evidence Solutions, IMS Health, London, UK; [2]Worldwide Epidemiology, GSK, London, UK; [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School, Boston, MA, USA; [4]Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK.*

Background: Treatment response refers to the outcome of patients on a treatment compared with a comparison group receiving an alternative treatment or control condition. Response to treatment varies between patients—treatment response heterogeneity. Identifying types of patients who respond most positively to treatment can help improve patient health and reduce costs.

Despite the potential value of subgroup treatment response analysis, the area remains controversial. The most common approach involves a straightforward comparison of the means of outcome by subgroups. The primary concern with this approach is false-positive findings through multiple-testing. Alternative approaches include estimation of multiple regression models, where treatment–covariate interactions are included to capture subgroup differences. This approach typically neglects overfitting. Limitations with both approaches are exacerbated in the presence of many candidate covariates.

New methodologies are needed to identify important subgroup differences. These methods need to be robust to overfitting and perform well in high-dimensional settings. Some solutions may be available from the field of machine learning. Highly flexible learning algorithms are excellent at identifying important associations (which may involve interactions and/or non-linearities), whilst techniques such as regularisation and cross-validation are designed to minimise overfitting/false-positive results. These methods are equally applicable to randomised and non-randomised study designs.

Objectives: The objectives of this study were as follows:

- To describe the strengths and limitations of traditional statistical methods
- To assess the potential of possible innovative solutions from machine learning
- To illustrate key concepts through case studies/examples.

Description: This workshop will review challenges associated with subgroup analyses and explore how innovative methods could be better utilised. Case studies will be presented to demonstrate novel methods and stimulate discussion. The workshop will be highly interactive with opportunity for audience members to ask questions and share experiences. Speakers include experts in both classical and machine learning methods.

727. Worldwide Database Networks: Methodological Challenges for Observational Drug Effect Research

Samy Suissa[1], Richard Platt[2], Xavier Kurz[3], Olaf Klungel[5], Nicole Pratt[4], Edward Chia-Cheng Lai[6]. *[1]Canadian Network for Observational Drug Effect Studies (CNODES), McGill University, Montreal, Canada; [2]FDA Mini-Sentinel Project, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA, USA; [3]European Medicines Agency, Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), London, UK; [4]Asia Pacific Pharmacoepidemiology Network (AsPEN), University of South Australia, Adelaide, South Australia, Australia; [5]Utrecht University, The Netherlands; Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), London, UK; [6]National Cheng Kung bUniversity, Taiwan.*

Background: Computerized healthcare databases are now routinely used in pharmacoepidemiology to conduct studies of safety signals generated for many prescription drugs. Yet, even with large databases, these individual initiatives are often insufficient to study rare but serious adverse events, drugs used for infrequent diseases, commonly used drugs with modest effects, and the effects of medications soon after they enter the market when their use is not yet widespread. To address these limitations resulting from insufficient data, several initiatives involving the "pooling" of multiple databases have been introduced worldwide.

Objectives: In this symposium, we will present four multinational networks of pharmacoepidemiologists and databases that have been formed around the world specifically to address the challenge of insufficient data. This symposium will appeal to researchers interested in understanding the methodological complexities and scientific advantages of this futuristic approach to drug safety assessment, as well as to decision makers who will query the networks to use the resulting information.

Description: Each network has approached the problem in different ways, depending largely on the specific philosophy behind their creation and more importantly on the data accessibility constraints. The symposium will discuss and compare these approaches in terms of their scientific strengths and limitations. In addition, the symposium will present specific methodological challenges to the design and analysis of pooled database studies that these different network approaches have generated. Recent examples of drug safety issues will be discussed, including studies on statins, antidiabetic drugs, and oral anticoagulants.

728. Protecting and Promoting Public Health through Pharmacovigilance: Approaches for Measuring the Impact of Pharmacovigilance Systems

Peter Arlett[1], Xavier Kurz[1], Sebastian Schneeweiss[2], Andrew Roddam[3], June Raine[4], Gerald Dal Pan.[5] *[1]European Medicines Agency, London, UK; [2]Harvard Medical School, Boston, USA; [3]GSK, Uxbridge, UK; [4]MHRA, London, UK; [5]CDER, FDA, Silver Spring, USA.*

Background: Measuring performance and impact of pharmacovigilance systems is important for delivering a quality system and inform process improvement, but such measurement is one of the few areas in pharmacovigilance where well-defined methods are not fully established and their application is not systematic. It is difficult to demonstrate this impact and use this information in a feedback loop to improve methods, procedures, and performance. Methods need to be further developed and applied in a targeted but systematic way in order to check whether systems generate added value and justify and prioritize resource use and identify areas where efficiency and effectiveness could be improved. More specifically, ways to measure the outcomes of pharmacovigilance—both in terms of economic and health outcomes—need to be established and applied.

Objectives: The aim of this study was to present a framework for pharmacovigilance system impact assessment being developed for application in the European context and discuss measurement methods, outcome indicators, and perspectives from regulators, academics, and industry.

Description: Peter Arlett, Head of Pharmacovigilance at EMA, will chair the discussions. Four speakers will discuss different challenges for impact assessment of pharmacovigilance systems:

(1) An emerging approach for pharmacovigilance system impact assessment (Peter Arlett, EMA)
(2) Methodological challenges in addressing health and economic impact questions (Sebastian Schneeweiss, Harvard Medical School)

(3) Measurement in practice: which outcome indicators? (Xavier Kurz, EMA)
(4) How collaboration between stakeholders can leverage resources and enable good practice (Andrew Roddam, GSK).

In addition to the speakers, the panel will include June Raine (MHRA, UK) and Gerald Dal Pan (CDER, US FDA). Key questions will be discussed with the audience, for example,

- Why do we need to assess the impact of pharmacovigilance systems?
- What modifiable indicators can be measured? Are population health indicators useful?
- What is the role of pharmacoepidemiology?

The need for a working group to further identify or develop outcome indicators and methods will be discussed.

729. Identifying Cases in Electronic Healthcare Databases: Pitfalls and Best Practices

Stephan Lanes[1], Alexander M Walker[2,3], Kevin Haynes[1], Michele Jonsson Funk[4]. *[1]Safety and Epidemiology, HealthCore, Inc., Wilmington, DE, USA; [2]WHISCON, LLC, Newton, MA, USA; [3]IMEDS, Washington, DC, USA; [4]Epidemioloogy, University of North Carolina, Chapel Hill, NC, USA.*

Background: Electronic healthcare databases present special challenges to study design and analysis. Diagnostic codes may be absent or provisional, introducing outcome misclassification should the investigator treat codes as rigorously representing actual health of individuals.

Objectives: This workshop will assist researchers in developing case-identifying algorithms for database studies that account for the contexts within which codes may appear and that draw on ancillary information and external medical knowledge. The workshop will include presentations concerning clinical, database, and methodological considerations. Research problems will be posed to the audience, and potential solutions will be elicited from the audience and the panel.

Description: Clinical considerations will address the drivers of healthcare encounters, patterns of care, and terminology:

- After disease onset, what needs to occur for an event to be captured in a database?
- What kinds of conditions are best-suited for database research?
- What strategies can be used when conditions do not always lead to a healthcare encounter?

Database considerations include the types of information available to identify cases in different kinds of databases, including accuracy of information, spectrum of care and missing data, processes and incentives for data entry, and coding systems:

- How can electronic health record workflows and claims reimbursement rules affect completeness and accuracy of diagnoses?
- How can temporal changes in data collection and coding processes affect algorithm performance?
- How does accuracy vary according to data field and source of information?

Methodological aspects focus on assessing algorithm performance and the contribution of outcome misclassification error to overall study bias. We will describe the importance of validation and the transportability of validated algorithms across study settings:

- Why is it important to quantify algorithm performance?
- What conditions are necessary to use a validated algorithm from a different study in my research?
- How can statistical methods be used to quantify and reduce bias due to outcome misclassification?

730. Generating Real-world Safety and Effectiveness Evidence for Biosimilars: Current Issues and Methodological Considerations

Jaclyn L Bosco[1], Nancy A Dreyer[1], George Neyerpally[2], Jeffrey S. Brown[3]. *[1]Real-World & Late Phase Research, Scientific Affairs, Quintiles, Cambridge, MA, USA; [2]University of Maryland School of Law, Baltimore, MD, USA; [3]Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston, MA, USA.*

Background: Biologics are expensive, potentially life-altering therapies. The availability of biosimilars is expected to increase in light of the new regulatory approval pathway for biosimilars in the USA and forthcoming global patent and data exclusivity expirations. A biosimilar is defined as a highly similar version of an already authorized biologic. The potential for immunogenicity, different manufacturing processes, and the degree of heterogeneity of biosimilars results in uncertainty about their purity and real-world safety and effectiveness.

Objectives: The objective of this workshop is to provide an overview of biosimilars, including different stakeholder perspectives and practical considerations for designing postmarket safety and effectiveness

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studies. Researchers seeking additional expertise in understanding biosimilars and the generation of real-world evidence on biosimilars will benefit from attending this symposium.

Description: This symposium includes perspectives from industry, pharmacy, regulatory, payers, and academia. Dr. Nancy Dreyer will provide an introduction to biosimilars. Dr. Jaclyn Bosco will present an overview of biosimilar issues including naming conventions, approval of different delivery mechanisms, extrapolation of indications, and interchangeability. Dr. George Neyarapally will discuss the US regulatory, pharmacy, and state and public payer perspectives on these issues. Dr. Bosco and Dr. Catherine Panozzo will discuss the approaches to develop study designs, identify comparison groups, handle confounding, and select appropriate data sources for pharmacoepidemiologic studies of biosimilars. Dr. Bosco will present methodological considerations for patient registries and *de novo* data collection methods. Dr. Panozzo will present considerations when using existing and future data sources, such as Mini-Sentinel and Sentinel, and share viewpoints from personal interviews of commercial payers. Dr. Dreyer will summarize the issues and viewpoints. Participants will be invited to ask questions and provide their perspectives on generating real-world evidence for biosimilars.

731. Safety Surveillance of New Oral Anticoagulants within the Mini-Sentinel Program—Progress, Challenges, and Future Directions

Marsha E Reichman,[1] Dorothee Bartels,[2] Ryan M Carnahan,[3] Elizabeth A Chrischilles,[3] Joshua J Gagne,[4] Alan S Go,[5] Darren Toh.[6] *[1]U.S. Food and Drug Administration, Silver Spring, MD, USA; [2]Boehringer Ingelheim GmbH, Ingelheim, Germany; [3]University of Iowa, Iowa City, IA, USA; [4]Brigham and Women's Hospital, Boston, MA, USA; [5]Kaiser Permanente Northern California, Oakland, CA, USA; [6]Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA.*

Background: The FDA-funded Mini-Sentinel program is developing a national active safety surveillance system for marketed medical products. The program has created a distributed network of electronic healthcare databases that include more than 178 million individuals and 358 million person-years of longitudinal observation time as of end of 2014. FDA is using Mini-Sentinel to conduct population-based safety surveillance of several newer oral anticoagulants (NOACs).

Objectives: This symposium will cover (1) FDA's regulatory need for monitoring the safety of NOACs and how Mini-Sentinel is helping to achieve its regulatory mission; (2) a series of completed and ongoing surveillance activities of NOACs within Mini-Sentinel; and (3) comments and perspectives from external stakeholders about these surveillance activities.

Description: Mini-Sentinel employs a wide array of tools and approaches to monitor the safety of NOACs. These include rapid assessment using modularized analytic programs, one-time protocol-based assessment, and both one-time and sequential assessments using the newly developed Prospective Routine Observational Monitoring Program Tools (PROMPTs). The speakers will describe the rationale, design, and findings of several ongoing and completed surveillance activities of NOACs. A group of external stakeholders will provide their perspectives on these Mini-Sentinel activities.

(1) Introduction and aims of the symposium (Toh, 5 minutes)
(2) FDA's need and vision for Mini-Sentinel to help monitor the safety of NOACs (Reichman, 5 minutes)
(3) Existing analytic capabilities within Mini-Sentinel (Toh, 10 minutes)
(4) Rationale, design, and findings of complete and ongoing activities (40 minutes):
    a. Dabigatran—Rapid assessments using modularized analytic programs (Reichman)
    b. Dabigatran—A protocol-based cohort study in atrial fibrillation patients (Go/Gagne)
    c. Dabigatran—A one-time PROMPT assessment (Reichman)
    d. Rivaroxaban—A sequential PROMPT surveillance (Chrischilles/Carnahan)
(5) Comments from external stakeholders (15 minutes)
    a. Regulatory perspective (TBD)
    b. Industry perspective (Bartels)
(6) Discussion with panel and audience (15 minutes)

732. Step-by-step Algorithm for the Development and Internal Validation of a Clinical Predictive Tool Using Routinely Collected Data: 5-Year Absolute Risk of Hip Fracture in Type 2 Diabetic Patients

Cristian Tebé,[1,2] Gary Collins,[3] Ramon Cleries,[4] Andrew Judge,[3,5] Nigel Arden,[3,5] Cyrus Cooper,[3,5] Daniel Prieto-Alhambra.[3,5,6] *[1]Statistical Advisory Service, Bellvitge Biomedical Research Institute-IDIBELL,*

Universitat de Barcelona, Barcelona, Catalonia, Spain; [2]Agencia de Qualitat i Avaluacio Sanitaries de Catalunya, Generalitat de Catalunya, Barcelona, Catalonia, Spain; [3]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK; [4]Cancer Control and Prevention Group, Bellvitge Biomedical Research Institute-IDIBELL, Universitat de Barcelona, Barcelona, Catalonia, Spain; [5]MRC Lifecourse Epidemiology Unit, Southampton University, Southampton, UK; [6]SIDIAP Database, and GREMPAL Research Group, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain.

Background: Clinical prediction tools (CPT) are important to inform medical decisions. Routinely collected data are a potential source of information for the development of data-hungry CPTs. However, missing data and variable selection pose challenges to the creation of such tools based on electronic records.

Objectives: The objectives of this study were to implement a step-by-step algorithm to develop and internally validate a CPT for the prediction of 5-year absolute hip fracture risk amongst type 2 diabetic patients based on routinely collected data and to evaluate performance of the CPT.

Methods: Computerised records (www.sidiap.org) linked to hospital admissions for all participants aged >40 years with a diagnosis of type 2 diabetes were analysed. Cox regression was used to derive a CPT following these steps: (1) descriptive analysis; (2) multiple imputation of 10 datasets; (3) each imputed data set was sampled with replacement 100 bootstraps; (4) in each of the resulting 1000 samples, a model was fitted using backward stepwise (p exit 0.157); (5) predictors retained in >70% of the models were considered for the final tool; (6) a CPT was derived with the resulting coefficients and standard errors following the combination rules by Rubin; (7) Harrell's concordance statistic for discrimination was calculated; and (8) calibration was examined graphically by comparing observed versus expected fractures by tenths of predicted risk

Results: Predictors included in the final model were age, sex, time since diabetes onset, body mass index, hip fracture history, cardiovascular disease, osteoarthritis, cataracts, glomerular filtration rate, falls, use of statins and insulin-therapy. The model showed good discrimination ($C = 0.81$) and calibration.

Conclusions: A step-by-step modelling strategy to develop a CPT for avoiding common pitfalls in routinely collected data is presented. A simple score derived using these methods provides a valid risk prediction tool. External validation of the CPT must be conducted before considering its implementation.

733. Development and Validation of an Algorithm to Identify Prostate Cancer Related Mortality in Electronic Medical Records Using Natural Language Processing

Julia R DiBello,[1] Lauren P Wallner,[2,3] Chengyi Zheng,[3] Wei Yu,[3] Bonnie H Li,[3] Stephen K VanDenEeden,[4] Sheila Weinmann,[5] Debra Ritzwoller,[6] Kathryn Richert-Boe,[5] Stephen J Jacobsen.[3] *[1]World Wide Epidemiology, GlaxoSmithKline, Collegeville, PA, USA; [2]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; [3]Division of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, USA; [4]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; [5]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA; [6]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA.*

Background: Death due to prostate cancer can be difficult to determine, if based solely on codes from death records. Death from progression of disease and/or development of distal metastases often occurs many years after the initial diagnosis, making identification of these events difficult using standard diagnoses codes from administrative databases.

Objectives: The aim of this study was to develop an algorithm, identifying men whose death is attributable to progression or development of metastatic prostate cancer, using EMR data and natural language processing (NLP).

Methods: An electronic algorithm was developed, combining information from EMR data fields and unstructured text, using NLP, among men with a diagnosis of prostate cancer between 1992 and 2010 in a large cohort of men who were part of an ongoing study of prostate cancer mortality. Records were searched from diagnosis until death or loss to follow-up. Each NLP component of the algorithm was validated against manual review of a sample of the corresponding records. The algorithm was then applied in a random sample and classified deaths as probable,

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possible, or not due to prostate cancer; this classification was validated by chart review and physician adjudication of discordant cases. Finally, the algorithm was applied in the full study population.

Results: Preliminary results suggest sensitivities and specificities of >94% for all of the NLP algorithm components except for clinic notes identifying increasing pain due to the presence of metastases (specificity = 67%). Of the 1139 men with a coded cause of death other than prostate cancer and suggestive of being related to prostate cancer, 170 (14.9%) and 659 (57.9%) were considered to have deaths that were probably and possibly related to prostate cancer, respectively.

Conclusions: These results suggest NLP can be used to identify men with metastatic prostate cancer related mortality in an EMR more accurately than cause of death and metastatic cancer codes alone. The use of NLP as part of an automated determination of cause of death can help to improve the accuracy of algorithms used in cause-specific cancer mortality research.

734. Assessing the Generalizability of a Statistical Natural Language Processing Model for Pneumonia Surveillance

Christian M Rochefort,[1] Aman D Verma,[1] Tewodros Eguale,[1] Alan J Forster,[2] David L Buckeridge.[1] *[1]Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, QC, Canada; [2]Clinical Epidemiology, The Ottawa Hospital Research Institute, Ottawa, ON, Canada.*

Background: Natural language processing (NLP) models are increasingly used for disease surveillance in acute care hospitals, but limited information is available on their generalizability.

Objectives: We examined the generalizability of a statistical NLP model for identifying pneumonia from electronic health record (EHR) data.

Methods: We randomly sampled 4000 narrative reports of chest radiological examinations performed at a university health network (UHN) in Quebec (Canada) between 2008 and 2012. We manually identified pneumonia within each report, which served as our reference standard. We used a nested cross-validation approach to train and validate a support vector machine (SVM) model predicting pneumonia. This model was then applied to a random sample of 2281 narrative radiology reports from another UHN in Ontario (Canada), and accuracy was measured. The accuracy of the Quebec model, as applied to Ontario data, was compared with that of two alternative models: (1) a model retrained on Ontario data and (2) a model trained and validated using all available data (pooled Quebec–Ontario model).

Results: On manual review, 640 (16.0%) and 303 (13.3%) reports were pneumonia-positive in Quebec and Ontario data, respectively. The SVM model predicting pneumonia on Quebec data achieved 83% sensitivity (95%CI: 78–88%), 98% specificity (95% CI: 97–99%), and 88% PPV (95%CI: 83–94%). When applied to Ontario data, this model achieved 57% sensitivity (95%CI: 51–63%), 99% specificity (95%CI: 98–99%), and 86% PPV (95%CI: 80–90%). In comparison, the model retrained on Ontario data achieved 76% sensitivity (95%CI: 70–82%), 98% specificity (95%CI: 97–99%), and 86% PPV (95%CI: 82–91%), while the pooled Quebec–Ontario model performed worse than the Quebec model, but better than the Ontario one.

Conclusions: The results of this study suggest that a statistical NLP model predicting pneumonia has limited generalizability when it is directly applied to EHR data from another institution. However, once this model has been recalibrated to local data, it can achieve good prediction performances.

735. Identification of Bone Metastases Using Administrative Claims, Electronic Medical Records (EMR), and Population Registries: Implications for Pharmacoepidemiology Research

Rohini K Hernandez[1], Alexander Liede[1], Johnny Kahlert[2], Mette Nørgaard[2], Justyna Amelio[3], Vera Ehrenstein[2]. *[1]Center for Observational Research, Amgen, Thousand Oaks, CA, USA; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Center for Observational Research, Amgen, Uxbridge, UK.*

Background: Understanding misclassification of key variables in a database is critical when deciding to what extent data can be used for pharmacoepidemiological studies. Accuracy of diagnostic coding in administrative claims databases and population-based registries is often unknown. We summarize both published and unpublished validation studies of bone metastases diagnostic codes to highlight that misclassification may vary by data source.

Objectives: The aim of this study was to validate diagnostic codes for bone metastases across varying data sources, evaluate an algorithm to capture missing cases, and discuss implications for research.

Methods: Diagnostic codes for bone metastases were validated against original clinical charts among men with prostate cancer in several different settings: administrative claims (ICD-9 in PharMetrics Plus [P+]), EMR from oncology clinics (ICD-9 in the Oncology Services Comprehensive Electronic Records [OSCER]), and the Danish National Registry of Patients (DNRP, ICD-10). Sensitivity (Se), specificity (Sp), and positive and negative predictive values (PPV and NPV) were estimated.

Results: Varying degrees of misclassification were observed across databases: (OSCER: PPV 92%, NPV 88%, Se 97%, Sp 70%; P+: PPV 95%, NPV 38%, Se 80%, Sp 75%; DNRP: PPV 100%, NPV 69%, Se 44%, Sp 100%). The US databases showed more false positives, while the Danish database had evidence of more false negatives. Algorithms using PSA values, receipt of bone scan, and antiresorptive therapy to identify missing patients with bone metastases in the DNRP were unsuccessful (all PPVs <30%).

Conclusions: The objective of a study should be a key consideration when selecting a data source. This case study implies that the Danish databases may be more accurate for comparative studies with bone metastases as an outcome given the perfect specificity but may underestimate prevalence. Conversely, the US data sources may overestimate prevalence. Analytic techniques can use bias analysis parameters such as sensitivity and specificity to quantify the extent of bias present in a study.

736. Identifying Idiopathic Pulmonary Fibrosis in a US Health Insurance Claims Database

Daina B Esposito,[1] Macarius Donneyong,[2] Crystal N Holick,[1] Stephan Lanes.[1] *[1]Safety and Epidemiology, HealthCore, Andover, MA, USA; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School, Boston, MA, USA.*

Background: Idiopathic pulmonary fibrosis (IPF) is a rare, irreversible interstitial pneumonia. Previous database studies used various case-identifying algorithms to estimate incidence and prevalence of IPF, but the performance of these algorithms has not been assessed.

Objectives: The aim of this study was to conduct a validation study to assess and improve the performance of case-identifying algorithms for IPF.

Methods: We used information obtained from the literature and consultation with clinical experts to develop two hierarchical IPF algorithms, and we applied them in the HealthCore Integrated Research DatabaseSM (HIRD) from 2006 to 2012. One algorithm was intended to be sensitive and the other, more specific. We then obtained medical records for a validation sample and had them adjudicated by clinical experts to determine case status, and we estimated the positive predictive value (PPV) for each algorithm. We also used the validation sample as a training data set to develop a logistic regression model using information in the HIRD to predict confirmed cases, and we used a second sample as a test data set to assess the performance of the model.

Results: We identified 4598 potential cases using the sensitive algorithm and 2052 (44.6%) patients using the specific algorithm. After medical record review, the PPVs of these algorithms were 54.0% (95%CI 39.3–68.2) and 57.6% (95%CI 44.8–69.7). The regression model identified 1384 (30.1%) cases and had a PPV of 83.3% (95%CI 69.8–92.5).

Conclusions: Automated claims databases are a valuable resource for studying rare diseases, but inaccurate and incomplete diagnostic codes can introduce outcome misclassification. To account for this uncertainty, previous IPF studies used sensitive and specific algorithms to estimate ranges of IPF frequency. This validation study found that both algorithms based on prior knowledge had low PPVs and after correcting for false positive errors, incidence and prevalence estimates decreased by about 45%. Combining regression modeling with internal validation can augment prior knowledge with empirical information from the claims database in developing an algorithm with increased PPV.

737. Evidence of Recent Statin Use Among "New" Statin Users in Medicare

Jessica Young,[1] Til Stürmer,[1] Michele Jonsson Funk.[1] *[1]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, USA.*

Background: Healthcare claims data are a rich resource in comparative effectiveness research and are often used to conduct retrospective new user cohort

studies. Few studies have evaluated the degree to which newly initiating statin users are correctly identified as such using claims data.

Objectives: The aim of this study was to examine the validity of identification of new users of statins using prescription claims.

Methods: Among Medicare Current Beneficiary Survey (MCBS) respondents, we identified patients with a new statin prescription after a 12-month washout period using Medicare Part D claims data from 2006 to 2009. Using MCBS survey data, we identified those with evidence of statin use (from interviewer review of bottles/receipts) in the 12 months prior to the index statin claim. Log-binomial regression was used to estimate adjusted prevalence ratios (adjPR) and 95% confidence intervals (CI) for the association between patient (age, race, gender, and low-income subsidy [LIS]) and prescription characteristics (index month and copay) and survey evidence of prevalent use. Calendar month was evaluated in 2-month intervals comparing each to September/October (referent).

Results: Among 684 new users of statins based on claims, 122 (18%) had evidence of recent statin use (prevalent users) based on survey data. Patients without LIS were 59% more likely to be prevalent users (adjPR = 1.59, CI: 1.02–2.48), and a $5 increase in copay was associated with a 3% increase in prevalent use (adjPR = 1.03, CI: 1.01–1.04). New users with an index claim in January/February were twofold more likely to have evidence of prevalent use during the prior 12 months than those in September/October (adjPR = 2.23, CI: 1.39–3.56); all other calendar intervals were similar to September/October.

Conclusions: Nearly 20% of individuals identified as new statin users (based on claims data) had evidence of statin use during the washout period. Higher-income patients and those with initiation dates in the first 2 months of the calendar year appear more prone to misclassification. Given the importance of the new user design for minimizing healthy user bias, further research is needed to assess the degree of and reasons for misclassification of new users in claims data and the extent to which this may bias effect estimates.

738. Comparative Effectiveness and Safety of Clozapine versus Standard Antipsychotic Treatment in Adults with Treatment-resistant Schizophrenia

Tobias Gerhard,[1,2] TS Stroup,[3] Cecilia Huang,[2] Stephen Crystal,[2] Mark Olfson.[3] *[1]Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA; [2]Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA; [3]Department of Psychiatry, Columbia University, New York, NY, USA.*

Background: Thirty percent of patients with schizophrenia receive little benefit from standard antipsychotic medications (APMs) and are considered to have treatment resistance, which is associated with marked disability and repeated hospitalizations. Clozapine is the only APM approved for treatment-resistant schizophrenia, but questions remain about its effectiveness and safety in clinical practice.

Objectives: The aim of this study was to compare the effectiveness and safety of initiating clozapine or a standard APM in adults with evidence of treatment-resistant schizophrenia.

Methods: Using national US Medicaid data from 2001 to 2009, we examined treatment outcomes of a retrospective cohort of adults with evidence of treatment-resistant schizophrenia that initiated clozapine ($n = 3123$) and a corresponding 1:1 propensity score-matched cohort that initiated a standard APM. New initiation was defined as no exposure to the index drug in the previous year. Treatment resistance was defined for the year prior to the index date as ≥1 mental disorder hospitalization, use of ≥2 different standard APMs, and an APM medication possession ratio of >0.75. Primary outcome was hospitalization for a mental health reason. Secondary outcomes included index treatment discontinuation, additional APM use, incidence of serious medical conditions, and death. Data were analyzed using Cox regression.

Results: Clozapine initiation was associated with decreased risk of hospitalization (HR 0.78; 95%CI, 0.68–0.82), index treatment discontinuation (HR 0.60; 0.55–0.65), and additional APM use (HR 0.76; 0.70–0.82), but not with lower mortality (HR 1.15; 0.75–1.77). Clozapine was associated with increased risk of diabetes mellitus (HR 1.41; 1.01–1.96), hyperlipidemia (HR 1.24; 1.05–1.46), and intestinal obstruction (HR 1.94; 1.08–3.49).

Conclusions:]In adults with schizophrenia with evidence of treatment resistance, initiating clozapine compared with a standard APM was associated with greater effectiveness on several important outcomes

as well as increased risk for several medical complications. Contrary to prior observational studies, there was no evidence that clozapine was associated with decreased mortality.

739. Benzodiazepines (BZPs) and the Risk of All-cause Mortality in Adults

Elisabetta Patorno,[1] Robert Glynn,[1] Moa Park,[1] Raisa Levin,[1] Krista Huybrechts.[1] [1]*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.*

Background: Recent evidence has suggested BZDs may be associated with over threefold increase in mortality risk. Most studies have used a non-active comparator group (non-users), without careful consideration of barriers to treatment in non-users, and have not properly accounted for channeling bias.

Objectives: The aim of this study was to evaluate the risk of mortality associated with BZD initiation versus non-initiation in adults, trying to address treatment barriers and channeling bias.

Methods: From a large, nationwide US commercial healthcare database, we identified patients who initiated a BZD between 2004 and 2013, and for each initiator, up to 10 non-initiators with a medical visit ±14 days of the BZD start (index date). We restricted to patients with no BZD use in the prior 6 months but required ≥1 filling for any other medication in the 90 days and 91–180 days before the index date, in an attempt to limit chances of treatment barriers. To reduce channeling bias, 1:1 propensity score (PS)-matched analyses were used to balance >100 baseline characteristics and to evaluate the risk of all-cause mortality among BZD initiators versus non-initiators in an intention-to-treat analysis over 6-month follow-up. In sensitivity analyses, to further reduce chances of treatment barriers and channeling bias, we included 200 additional empirically selected variables in 1:1 high-dimensional (hd)-PS-matched analyses, and compared BZD initiators with an active comparator group (initiators of SSRI antidepressants).

Results: In a PS-matched population of 1 256 630 patients per exposure group with median (IQR) age = 46 years (35, 55) for BZD initiators and 47 years (35, 57) for non-initiators, the incidence rate for all-cause mortality was 8.4/1000 py and 9.6/1000 py, respectively. The Cox hazard ratio (HR) associated with BZD initiation versus non-initiation was 0.89 (95%CI, 0.85–0.93). The HR moved to 1.00 (0.96–1.04) in the 1:1 hd-PS-matched population and to 1.12 (1.07–1.16) when BZD initiators were compared with SSRI new users.

Conclusions: This large cohort study suggests either no increase or a modest increase in the risk of mortality associated with BZDs. If a detrimental effect with regard to mortality exists, it is unlikely to exceed a 16% risk increase.

740. Can Selective Serotonin Reuptake Inhibitors Increase Cataract Risk? Results from a Case–Control Analysis

Claudia Becker[1], Susan S Jick[2], Christoph R Meier[1,2,3].

[1]*Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland;* [2]*Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA;* [3]*Hospital Pharmacy, University Hospital Basel, Basel, Switzerland.*

Background: Little is known about the association between antidepressant drugs and cataract risk. Amitriptyline exposure was reported to increase the risk of cataract. Animal studies have identified serotonin receptors in the lens and provided evidence that serotonin may increase lens opacity. One population-based study reported a slightly increased cataract risk for current users of selective serotonin reuptake inhibitors (SSRI) (RR 1.15, 95%CI 1.08–1.23). However, results were not adjusted for smoking.

Objectives: The aim of this study was to explore the association between the use of SSRI and the risk of cataract.

Methods: We conducted a case–control analysis within the UK-based Clinical Practice Research Datalink (CPRD). Cases were ≥40 years and either had an incident cataract diagnosis or a recorded cataract extraction (i.e., the index date). Up to four controls per case were matched on age, sex, calendar time, general practice, and number of years of history in the CPRD prior to the index date. We assessed the number of SSRI prescriptions before the index date and

conducted conditional logistic regression to derive odds ratios (ORs) with 95% confidence intervals (CI). The contribution of various potential confounders including co-morbid conditions as well as exposure to other drugs previously associated with cataract development was evaluated in univariate models, and final results were adjusted for BMI, smoking, hypertension, diabetes, glaucoma, oral steroids, and other antidepressants.

Results: A total of 158 679 cataract cases and 564 787 matched controls were identified. Long-term use (≥20 prescriptions) of SSRI was not associated with an altered risk of cataract (adj. OR 0.97, 95%CI 0.94–1.00) nor was current long-term use (i.e., last prescription within 6 months before the index date¸ adj. OR 0.98, 95%CI 0.95–1.02). In accordance with previous studies, we found a slightly increased cataract risk for users of tricyclic antidepressants (adj. OR 1.13, 95%CI 1.10–1.16), which was the highest for amitriptyline (adj. OR 1.22, 95%CI 1.20–1.24) and nortriptyline (adj. OR 1.39, 95%CI 1.25–1.55).

Conclusions: According to our study, SSRI use is not associated with cataract development.

741. Serotonin-norepinephrine Reuptake Inhibitors and the Risk of Acute Kidney Injury: A Cohort Study of Eight Administrative Databases and Meta-analysis

Christel Renoux,[1,2] Lisa M Lix,[3] Valérie Patenaude,[1] Lauren C Bresee,[4] Michael J Paterson,[5] Jean-Philippe Lafrance,[6] Hala Tamim,[7,8] Salaheddin M Mahmud,[9] Wasem Alsabbagh,[10] Brenda Hemmelgarn,[11] Colin R Dormuth,[12] Pierre Ernst,[1,13] The CNODES Investigators.[1] *[1]Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, Montreal, QC, Canada; [2]Department of Neurology, McGill University, Montreal, QC, Canada; [3]Community Health Sciences, College of Medicine, University of Manitoba, Winnipeg, MB, Canada; [4]School of Public Health, University of Alberta, Edmonton, AB, Canada; [5]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [6]Centre de Recherche Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; [7]School of Kinesiology and Health Science, York University, Toronto, ON, Canada; [8]Department of Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada; [9]Winnipeg Regional Health Authority, Winnipeg, Manitoba, Canada, Vaccine and Drug Evaluation Centre, Department of Community Health Sciences, University of Manitoba, Winnipeg Faculty of Pharmacy, University of Manitoba, Winnipeg, MB, Canada; [10]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada; [11]Community Health Sciences, Department of Medicine, University of Calgary, Calgary, AB, Canada; [12]Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Vancouver, BC, Canada; [13]Department of Medicine, Pulmonary Division, Jewish General Hospital, Montreal, QC, Canada.*

Background: Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressants that are widely used as a first-line treatment for depression and anxiety disorders. However, recent evidence suggests that SNRI use may be associated with acute kidney injury (AKI).

Objectives: The purpose of this study was to determine if exposure to SNRIs was associated with an increased risk of AKI in comparison with selective serotonin reuptake inhibitors (SSRIs) and assess the risk associated with specific SNRIs.

Methods: We conducted a retrospective population-based cohort study, with a nested case–control approach in eight administrative databases from Canada, the United States, and the United Kingdom. The study cohort consisted of all new users of SNRIs and SSRIs, aged 12 years or older with a first prescription for an SNRI or SSRI between 1 January 1997 and 31 March 2010. For each case (a patient hospitalized for AKI), up to 10 controls were randomly selected, matching on age, sex, and calendar time. Current exposure to SNRIs/SSRIs was defined as a prescription lasting until the index date or dispensed in the 60 days preceding the index date. The incidence rate ratios (RR) of SNRIs compared with SSRIs were estimated using conditional logistic regression, with adjustment for high-dimensional propensity scores at baseline. Meta-analytic methods were used to estimate the net effect across sites.

Results: The study cohort included 557 476 new users of SNRIs and 2 698 050 new users of SSRIs. During follow-up, 38 974 cases of AKI occurred and were matched with 384 034 controls. The use of SNRIs was not associated with an increased risk of AKI (pooled RR 0.97; 95%CI 0.94, 1.01). Similarly, no association was found with both venlafaxine and desvenlafxine considered together (RR 0.96; 95%CI 0.92, 1.00). Dulexotine use was associated with a 16% increase in risk (RR 1.16; 95%CI 0.96, 1.40), which after further adjustment, was reduced to 1.02 (95%CI 0.95, 1.10).

Conclusions: Our results suggest that SNRI use is not associated with an increased risk of AKI compared with SSRIs.

742. The Risk of Ischemic Cardiovascular Events Associated with Oxycodone/Naloxone and Other Extended-release High-potency Opioids

Kathrin Jobski,[1] Bianca Kollhorst,[2] Edeltraut Garbe,[1] Tania Schink.[1] *[1]Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany; [2]Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany.*

Background: In 2012, concerns were raised regarding possible cardiovascular (CV) risks associated with opioid antagonists indicated for the treatment of opioid-induced constipation (OIC). In Germany, an extended-release (ER) combination of the high-potency opioid (HPO) oxycodone and the opioid antagonist naloxone was approved in 2006. It is indicated in the EU for the treatment of severe pain while improving OIC.

Objectives: The aim of this study was to estimate the risk of ischemic CV events in patients prescribed oxycodone/naloxone (OXYN) compared with those receiving other ER HPOs including patches.

Methods: Using data from the German Pharmacoepidemiological Research Database (GePaRD), we identified a cohort of ER HPO users. Cohort entry was set to the first ER HPO dispensation between 2006 and 2011. The outcome was defined as hospitalization for either acute myocardial infarction (MI) or ischemic stroke (IS). We calculated incidence rates (IRs) with 95% confidence intervals (CIs). Within this cohort, we conducted a nested case–control analysis to obtain confounder-adjusted odds ratios (aORs) for the risk of MI/IS associated with (i) current ER HPO use; (ii) recent discontinuation; or (iii) recent switch of ER HPO treatment.

Results: During the study period 309 936 patients received at least one ER HPO. Mean age at cohort entry was 70 years, and 67% were female. Overall, 12 384 CV events were observed resulting in an IR of 19.48 (95%CI: 19.14–19.82) per 1000 person years. The highest IR was found for fentanyl (24.99; 24.03–25.98), whereas use of OXYN was associated with a lower risk (19.03; 17.41–20.76). In the case–control analysis, only current morphine use yielded a small but significantly elevated aOR of 1.12 (1.04–1.22) for MI/IS compared with past use. Recent discontinuation and recent switch of any ER HPO had a statistically significant impact as well (aOR: 1.12; 1.04–1.21 and 1.25; 1.03–1.52, respectively).

Conclusions: In a cohort of nearly 310 000 ER HPO users, no elevated risks of MS/IS were observed for OXYN use compared with other ER HPOs. Overall, our study does not indicate an association between opioid antagonists indicated for OIC treatment and major CV events.

743. Tempest in a TE-Cup: A Case of Publication Bias in Pharmacoepidemiology

Marc B Stone,[1] Victor Crentsil.[1] *[1]US Food and Drug Administration, Silver Spring, MD, USA.*

Background: Most published observational studies show an association between antipsychotic use and thromboembolism (TE).

Objectives: The objectives of this study were to (1) consider the possible role of publication bias and (2) to compare the published literature with results obtained from prospective studies in drug development programs.

Methods: Random effects meta-analysis of a published literature search with meta-regression to test and correct for small study effects was carried out.

All studies of antipsychotic drugs using human subjects submitted to the FDA were reviewed for TE events. Random effects negative binomial regression was used to calculate pooled incidence rates and incidence rate ratios.

Results: Seventeen of 18 published observational studies reported a relative risk greater than one; 12 were statistically significant. The random effects pooled estimate for antipsychotic-associated relative risk for VTE was 1.58 (95%CI: 1.36–1.82). There was a strong positive correlation (0.77) between the logarithm of relative risk and its standard error ($p = 0.0004$), suggesting publication bias. When corrected for standard error, the relative risk was 1.11 (95%CI: 0.83–1.48).

In 300 placebo-controlled trials of antipsychotics performed by pharmaceutical manufacturers ($N = 76\,242$), there were only 12 TE cases, an incidence rate of 1.4 cases per 1000 person-years. The incidence rate among antipsychotic-treated subjects was

numerically lower than placebo. Among 807 studies without placebo controls ($N = 163\,369$), the incidence rate was 1.7 cases per 1000 person-years. The incidence rate ratio for TE, comparing studies with no placebo control to the placebo-controlled studies, was 1.26 (95%CI: 0.63–2.51).

Conclusions: The evidence for antipsychotic drugs causing TE is equivocal at best. The plethora of publications suggesting an association appears to be a consequence of publication bias: studies with small standard errors generally indicate at most a small effect. In clinical trials of antipsychotics, the rate of TE among antipsychotic users was quite low and no higher than the rate with placebo. The clinical trial data, however, do not rule out a higher relative risk, but any plausible increase in TE risk is unlikely to be of clinical significance.

744. A Cohort of Alzheimer Disease and Dementia Cases from Administrative Data: First Results on Prevalence, Incidence and Mortality

Edeltraut Kröger,[1,2] Louis Rochette,[3] Christian Bocti,[4] Robert Laforce, Jr.,[1,2] Éric Pelletier,[3] Valérie Émond.[3]
[1]Université Laval, Québec, Canada; [2]Centre d'Excellence sur le Vieillissement de Québec, CR-CHU de Québec, Québec, Canada; [3]Institut National de Santé Publique du Quebec, Québec, Canada; [4]Université de Sherbrooke, Sherbrooke, Canada.

Background: In 2011, Alzheimer disease (AD) and dementia affected 747 000 Canadians. Frequency estimates for AD/dementia are mostly based on the Canadian Study of Health and Aging (CSHA, 1991–2001). Administrative data are increasingly used for the surveillance of chronic diseases, including AD/dementia, and may add insight into care trajectories.

Objectives: The objectives of this study were to test three algorithms for the identification of a Quebec cohort of AD/dementia cases from linked health administrative data and to calculate incidence, prevalence, and mortality from 1998 to 2012.

Methods: The study used data from (1) the RAMQ medical and pharmaceutical services and the registered users' files; (2) the MED-ECHO hospital discharge file; and (3) the death registry, linked at the Institut national de santé publique du Québec. AD/dementia cases were identified using three different combinations of ICD dementia-related diagnostic codes from physicians or hospital discharge, with or without pharmacy claims for four dementia medications. Sensitivity and specificity of the three definitions were assessed by the Public Health Agency of Canada. Estimates were age-standardized.

Results: The study included 1.3 million persons aged 65+ years. In 2011–2012, 6.8% to 10% among them were identified as cases, depending on the definition. Prevalence was 15% to 18% higher among women than men and rose exponentially in older age groups. About 1% to 2.5% of persons aged 65 to 69 years were identified as cases, compared with 27% to 35% for persons 85+ years. Incidence rates varied between 16.5 and 21.7 per 1000 person-years depending on the definition. Highest incidence rates were measured in 2006–2007 for all three definitions. Mortality rate ratios between those affected by AD/dementia and the unaffected varied between 4.2 and 4.7, depending on the definition.

Conclusions: These frequency estimates are lower than extrapolations from the CSHA, possibly due to underreporting in administrative data. Different data sources for incidence and prevalence estimates are used in Canada, challenging their interpretation. Surveillance from health administrative data is feasible and useful for research on service and medication use.

745. Sex-specific Associations for Predicting Psychotropic Drug Use in Older Adults with Cognitive Impairment

Daniela C Moga,[1,2] Danijela Gnjidic,[3] Gregory Jicha.[4]
[1]Department of Pharmacy Practice and Science, University of Kentucky, Lexington, KY, USA; [2]Department of Epidemiology, University of Kentucky, Lexington, KY, USA; [3]University of Sydney, Sydney, Australia; [4]University of Kentucky, Lexington, KY, USA.

Background: Despite safety concerns, older people with cognitive impairment commonly use psychotropic drugs. Identifying sex-specific risk factors for psychotropic use could help guide targeted intervention to optimize medication use in this population.

Objectives: The aim of this study was to examine sex as a predictor of psychotropic drug use in older adults with cognitive impairment.

Methods: A retrospective cohort study using data collected during 2005–2014 as part of the prospective

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and standardized clinical evaluation of subjects enrolled in the National Alzheimer's Coordinating Center cohort was performed. We identified participants 65 years and older with either mild cognitive impairment (MCI) or dementia during cohort enrollment. Psychotropic drug use was defined based on participants reporting either an antipsychotic, anxiolytic, sedative, or hypnotic drug at the index visit during cohort enrollment. Logistic regression with backward elimination was performed to investigate the role of sex as predictor and modifying factor, identify other predictors of psychotropic drug use, and determine the odds ratios (OR) with associated 95% confidence intervals (CI).

Results: Of the 3664 participants (1693 men, 1971 women) with MCI or dementia, 13.5% ($n=493$; 210 men, 283 women) reported psychotropic use. In unadjusted analysis, compared with women, men over 85 years were less likely to use psychotropic drugs (8.6% vs 13.1%; $p=0.03$). Women using psychotropic drugs were more likely to live in nursing homes (10.6% vs 7.62%, $p=0.007$). After adjusting for important predictors including age, body mass index, level of independence, and residence type, sex remained a significant predicting factor, with statistically significant interaction between sex and the presence of delusions: women with delusions were less likely (OR=0.43, 95%CI:0.21–0.89), while women without were more likely (OR=1.35, 95%CI:1.08–1.69) to report psychotropic use.

Conclusions: The findings of this study indicate that sex is an independent predictor of psychotropic drug use in older people with cognitive impairment; thus, it is important to consider gender when optimizing pharmacological treatments in older adults with cognitive impairment.

746. Cumulative Use of Strong Anticholinergic Medications and Incident Dementia

Shelly L Gray,[1] Melissa L Anderson,[2] Sascha Dublin,[2,3] Joseph T Hanlon,[4] Rebecca Hubbard,[5] Rod L Walker,[2] Onchee Yu,[2] Paul Crane,[6] Eric B Larson.[2,6] *[1]School of Pharmacy, University of Washington, Seattle, WA, USA; [2]Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA; [3]Department of Epidemiology, University of Washington, Seattle, WA, USA; [4]Division of Geriatric Medicine, University of Pittsburgh, Pittsburgh, PA, USA; [5]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA; [6]Division of General Internal Medicine, University of Washington, Seattle, WA, USA.*

Background: Many medication classes have anticholinergic effects, which may cause cognitive impairment. This impairment has generally been thought to be reversible upon discontinuation. However, some studies suggest that these medications may increase dementia risk.

Objectives: The aim of this study was to examine whether higher cumulative use of anticholinergic medications is associated with a higher risk of incident dementia.

Methods: Data came from a prospective population-based cohort study, Adult Changes in Thought (ACT), set within Group Health, an integrated healthcare delivery system in the northwest USA. These analyses included 3434 participants aged 65 years and older who were community dwelling and free of dementia at study entry and who had at least 10 years of prior GH enrollment. Initial recruitment occurred between 1994 and 1996, and recruitment and follow-up have continued since that time. Cognitive screening is performed every 2 years, and low scores trigger further evaluation. Diagnoses of incident dementia and Alzheimer's disease (AD) are assigned by a multidisciplinary consensus committee using standard diagnostic criteria. From computerized pharmacy dispensing data, cumulative anticholinergic exposure (time-varying) was defined as the total standardized daily doses (TSDD) dispensed in the past 10 years. Use in the most recent 12 months was excluded to avoid use related to prodromal symptoms. Statistical analyses used Cox proportional hazards models, adjusted for demographics, health behaviors, and health status including comorbidities.

Results: Over a mean follow-up of 7.3 years, 797 participants (23%) developed dementia (637 developed AD). A 10-year cumulative dose–response relationship was observed for both dementia and AD ($p<0.001$). For dementia, adjusted hazard ratios and 95% confidence intervals (CI) were 0.92 (95%CI, 0.74–1.16) for 1–90 TSDD compared with nonuse; 1.19 (0.94–1.51) for 91–365 TSDD; 1.23 (0.94–1.62) for 366–1095 TSDD; and 1.54 (1.21–1.96) for >1095 TSDD. Results were similar for AD.

Conclusions: Higher cumulative use of anticholinergic medications is associated with an increased risk for dementia. Patients and providers should be aware of this potential risk.

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747. Comparative Effectiveness of Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB) for the Risk of Dementia in Patients With Type 2 Diabetes Mellitus and Hypertension

Hemalkumar B Mehta,[1] Vinay Mehta,[2] Chu-Lin Tsai,[3] Hua Chen,[4] Rajender Aparasu,[4] Michael L Johnson.[4]
[1]Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA; [2]Epidemiology, Merck, North Wales, PA, USA; [3]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Pharmaceutical Health Outcomes and Policy, University of Houston, Houston, TX, USA.

Background: Older patients with type 2 diabetes (T2DM) and hypertension (HTN) are at high risk of developing dementia, and angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) may reduce the risk of dementia. However, the comparative effectiveness of ACE versus ARB in protecting against dementia has not been well established using observational data.

Objectives: The aim of this study was to compare the effectiveness of ACE inhibitors and ARB on the risk of dementia in patients with T2DM and HTN using time-dependent Cox regression and marginal structural models (MSM).

Methods: This retrospective cohort study used the Clinical Practice Research Database from 2002 to 2012 and included elderly patients (age ≥ 65 years) diagnosed with type 2 diabetes and hypertension. Incident users of ACE inhibitors and ARB without prior dementia were included. All patients were followed for up to 10 years to observe dementia. Hazard ratio (HR) estimates for ARB versus ACE inhibitors from an MSM were compared with estimates from a time-dependent Cox model. Both models included primary exposure and time-independent confounders such as demographic characteristics, 30 comorbidities, and over 13 clinical variables including blood pressure. The MSM controlled time-dependent blood pressure using inverse probability of treatment weights.

Results: The study included 32 856 patients (mean age 71.55 years ± 7.86; 53% male). A total of 915 patients (2.79%) developed dementia during the follow-up. The unadjusted (OR, 0.86; 95%CI, 0.73–1.01) and Cox regression model (OR, 0.88; 95%CI, 0.75–1.04) showed no difference between ACE inhibitors and ARB, whereas the MSM showed that ARB offered 39% (OR, 0.61; 95%CI, 0.50–0.77) reduction in the risk of developing dementia compared with ACE inhibitors.

Conclusions: Time-dependent confounding due to blood pressure should be adjusted for when estimating the effectiveness of antihypertensive drugs on the risk of dementia. ARB may offer a protective effect on the risk of dementia compared with ACE inhibitors in patients with type 2 diabetes and hypertension.

748. Burden of Medications on Sleep Outcomes in Older Adults in the USA

Dima M Qato.[1] *[1]Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago, Chicago, IL, USA.*

Background: Medications are widely used, and many have side effects that affect sleep outcomes, particularly insomnia and somnolence. While insomnia and restless sleep are common among older adults, there is limited information on the association between medication use and sleep outcomes.

Objectives: The aim of this study was to examine whether the use of multiple medications with insomnia or somnolence side effects is associated with restless sleep and sleep latency, respectively.

Methods: We used a nationally representative population-based sample of 3129 community-dwelling older adults aged 57 to 85 years for 2012 in the USA. We conducted analyses using multivariate linear and logistic regression to examine the cross-sectional association between the use of multiple medications (prescription and non-prescription) that have insomnia and somnolence side effects and measures of sleep onset latency (time [in minutes] to fall asleep) and restlessness during sleep. Micromedex was used to identify medications with sleep side effects.

Results: Among the 3129 older adults in the sample, more than 57% and 39% use at least one medication with a somnolence and insomnia side effect, respectively. More than 20% regularly used three or more medications with somnolence side effects, which was associated with a significant decline in sleep onset (−3.4 minutes; p-value < 0.05). The number of medications used with insomnia side effects was associated with restless sleep; older adults using one to two and

three or more medications with insomnia side effects were 1.5 and 2.1 times more likely to report restless sleep (OR 1.5 [95%CI 1.3,1.8] and OR 2.1 [1.2, 3.5], respectively).

Conclusions: Medications with sleep side effects are frequently used and influence sleep outcomes in older adults, specifically insomnia and sleep onset latency. Efforts to improve sleep outcomes, and ultimately healthy aging, should incorporate an evaluation of the risks of medications based on their sleep side effects.

749. Medication Regimen Complexity and Polypharmacy as Factors Associated with Unplanned Hospitalization: A Population-based Cohort Study in Older People in Sweden

Barbara C Wimmer,[1] J Simon Bell,[1,2] Johan Fastbom,[3] Michael D Wiese,[2] Kristina Johnell.[3] *[1]Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Vic, Australia; [2]Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia; [3]Aging Research Center, Karolinska Institute and Stockholm University, Stockholm, Sweden.*

Background: Adverse drug events are a leading cause of preventable hospitalization among older people. The possible association between medication regimen complexity and unplanned hospitalizations has not been investigated in population-based studies.

Objectives: The aim of this study was to investigate and compare the associations between medication regimen complexity and polypharmacy with unplanned hospitalization over a 3-year period.

Methods: This population-based study analyzed data from 3348 participants aged 60 years and over in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). Medication regimen complexity was assessed using the 65-item Medication Regimen Complexity Index (MRCI) in 10-unit steps. Polypharmacy was assessed by using the number of medications as continuous variable. Cox proportional hazard models were used to compute unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for factors associated with unplanned hospitalization over a 3-year period. Receiver operating characteristics (ROC) curves and corresponding areas under the curve (AUCs) were calculated for the association between MRCI and polypharmacy with unplanned hospitalization.

Results: In total, 1125 people (33.6%) had one or more unplanned hospitalizations over a 3-year period. When adjusted for age, sex, education, living place, co-morbidity, activities of daily living, mini-mental state examination, unplanned admission in the previous year, self-reported pain, dexterity, and receipt of help to sort medications, medication regimen complexity (HR 1.22; 95%CI 1.14–1.34) and polypharmacy (HR 1.07; 95%CI 1.04–1.09) were both associated with unplanned hospitalization. The AUCs were similar for both medication regimen complexity and polypharmacy.

Conclusions: Medication regimen complexity and polypharmacy were both associated with unplanned hospitalization. Both parameters had a similar ability to predict unplanned hospitalization.

750. Cardiac Disorders in Patients with Myeloproliferative Neoplasm

Jasmanda H Wu,[1] Ling Zhang,[1] Stephen Lin,[1] Juhaeri Juhaeri.[1] *[1]Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, USA.*

Background: Myeloproliferative neoplasms (MPN) include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Janus kinase 2 (JAK2)^{V617F} is the most commonly recognized mutation in MPN. Previous studies showed that patients with JAK2^{V617F} mutation had a higher probability of developing future CV events. MPN predominantly affects elderly patients, and elderly patients have higher burden of CV comorbidities and mortality. Patients with MPN may be at higher risk of developing CV events.

Objectives: The aim of this study was to estimate the incidence of congestive heart failure (CHF), acute myocardial infarction (AMI), and cardiac arrhythmia among patients with MPN and compare it with those without MPN.

Methods: Patients with a diagnosis of MPN were identified from 1 January 2003 to 31 March 2013 using the US MarketScan database. The control cohort consisted of a random sample matched to the MPN cohort by age and gender in a 1:1 ratio. Diagnosis of

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CHF was ascertained using ICD-9-CM 428.x. Diagnosis of AMI was ascertained using ICD-9-CM 410.x0 or 410.x1. The ICD-9-CM codes of 427.x or 798.x were used to identify cardiac arrhythmia. Cox proportional hazards modeling was used to compare the rates between two cohorts.

Results: A total of 39 761 MPN patients, including PV (51%), ET (42%), post-PV MF (0.2%), post-ET MF (1%), and PMF (2.8%) were identified. Approximately 27% of them were >65 years of age, and 51% were male. Patients with MPN had higher rates of cardiac events, compared with those without MPN (CHF: MPN vs. non-MPN: 9.27 vs. 3.70/1000 person-year, HR = 1.64, 95%CI 1.42–1.88; AMI: MPN vs. non-MPN: 10.45 vs. 5.02/1000 person-year, HR = 1.44, 95%CI 1.27, 1.63; cardiac arrhythmia: MPN vs. non-MPN: 106.5 vs. 53.9/1000 person-year, HR = 1.42, 95%CI 1.36–1.48). The association was also present in patients without a history of cardiac disorders. Results from additional analysis using a propensity score matching method were similar.

Conclusions: Patients with MPN had higher incidence rates of CHF, AMI, and cardiac arrhythmia, compared with those without MPN. Clinicians should be aware of high occurrence of cardiovascular complications in patients with MPN.

751. Diabetes, Pancreatitis, and Pancreatic Cancer Risk: Implications for Study of Associations Between Diabetes Medications and Pancreatic Cancer

David J Graham,[1] Lorene M Nelson,[2] Jeff Yang,[3] Katlyn Calia,[3] Jason Wyman,[3] Andrew E Howery,[3] Thomas E MaCurdy,[2,3] Chris Worrall,[4] Jeffrey A Kelman[4]. *[1]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [2]Stanford University, Stanford, CA, USA; [3]Acumen, LLC, Burlingame, CA, USA; [4]Centers for Medicare & Medicaid Services, Washington, DC, USA.*

Background: To assess the association of diabetes medications with pancreatic cancer risk, it is critical to account for the underlying associations, if any, between diabetes, pancreatitis, and pancreatic cancer.

Objectives: The aim of this study was to determine the pattern of risk between diabetes duration, time since first pancreatitis, and pancreatic cancer.

Methods: We created a database of all Medicare-enrolled patients age ≥65 years residing in postal zip codes corresponding to SEER cancer registries for the years 1994–2013 and linked this with SEER registry files for all Medicare beneficiaries with an incident cancer from 2000 to 2009. We identified all cases of pancreatic cancer, and using incidence density sampling, we selected up to 10 controls per case matched on age, sex, race, length of Medicare enrollment, and county of residence. Incident diabetes was identified using a Medicare-validated algorithm (sen 84%, PPV 82%), and the first episode of pancreatitis was identified using ICD-9 coding. Conditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for pancreatic cancer in association with duration of diabetes and time since first pancreatitis, by yearly increments, adjusted for matching factors and other relevant covariates. We also examined the potential interaction between diabetes and pancreatitis on pancreatic cancer risk.

Results: There were 27 128 incident cases of pancreatic cancer and 260 130 matched controls. The OR (95%CI) of pancreatic cancer within 1, 1–2, or ≥2 years of diabetes onset was 3.27 (3.10–3.45), 1.79 (1.67–1.93), and 1.47 (1.41–1.53), respectively. For time since first episode of pancreatitis, the corresponding ORs were 19.14 (17.53–20.89), 3.20 (2.76–3.71), and 1.68 (1.54–1.82), respectively. Pancreatic cancer risk was markedly increased in the year following the onset of both diabetes and first episode of pancreatitis (OR = 48.3, 95%CI 36.4–64.1).

Conclusions: Diabetes and pancreatitis may both be consequences of and risk factors for pancreatic cancer. Studies of diabetes medications and pancreatic cancer should account for these complex relationships in their design and analysis.

752. Risk of Pancreatic Cancer Associated With Use of Incretin-Based Therapy and other Glucose-Lowering Agents: A Nationwide Case–Control Study in Denmark

Johnny Kahlert,[1] Diana H Christensen,[2] Reimar W Thomsen,[1] Søren T Knudsen,[2] Lars Pedersen,[1] Helene Nørrelund,[1] Olaf M Dekkers,[3] Ian Douglas,[4] Giulio Marchesini,[5] Liam Smeeth,[4] Niels Møller,[2] Henning Beck-Nielsen[6], Jens Otto L Jørgensen[2], Henrik T Sørensen[1]. *[1]Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University*

Hospital, Aarhus, Denmark; [2]Medical Department M (Endocrinology & Diabetes), Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark; [3]Leiden University Medical Center, Leiden, The Netherlands; [4]London School of Hygiene and Tropical Medicine & University College London, London, UK; [5]Alma Mater Studiorum University of Bologna & Bologna University Hospital, Bologna, Italy; [6]Danish Centre for Strategic Research in Type 2 Diabetes, Department of Endocrinology, Diabetes Research Centre, Odense University Hospital, Odense, Denmark.

Background: Incretin-based drugs (glucagon-like peptide 1 (GLP-1) mimetics and dipeptidyl peptidase 4 (DPP4) inhibitors) have been suspected to increase risk of pancreatic cancer.

Objectives: We examined if use of incretin-based drugs was associated with risk of pancreatic cancer and compared with other glucose-lowering agents.

Methods: Using population-based medical databases, this analysis was carried out as an age-matched, gender-matched, and residence-matched (1:10) case–control study from 2005 to 2012 (6036 pancreatic cancer cases and 60 360 controls). Odds ratios (ORs) for pancreatic cancer associated with use of incretin-based drugs and other glucose-lowering agents were computed, using conditional logistic regression, and we adjusted for other pancreatic cancer risk factors.

Results: A total of 122 incident pancreatic cancer patients (2.0%) versus 400 controls (0.7%) had used incretin-based drugs at least once, whereas 20.8% cases versus 8.6% controls had used any glucose-lowering agent. Patients with pancreatic cancer more often than controls had a hospital history of chronic pancreatitis (3.6% vs. 0.3%), gallstone (10.7% vs. 5.3%), obesity (4.0% vs. 2.9%), alcoholism (6.5% vs. 3.9%), and chronic pulmonary disease (21.2% vs. 17.9%). Compared with non-users of any glucose-lowering agents, the adjusted risk of pancreatic cancer was increased for DPP4 inhibitor users (adjusted OR = 3.87, 95%CI 3.06–4.89) and GLP-1 mimetic users (adjusted OR = 2.70, 95%CI 1.82–4.00), and furthermore, for every users of metformin (adjusted OR = 2.65, 95%CI 2.44–2.88), sulfonylureas 2.65 (2.41–2.91), and insulin (adjusted OR = 3.61, 95% CI 3.24–4.03). The highest cancer ORs were observed among new initiators of each glucose-lowering agent and in those with fewer than three prescriptions filled, suggesting a non-causal or reverse causal association.

Conclusions: The risk of pancreatic cancer was increased to similar levels for all glucose-lowering agents. This suggests that diabetes is a risk factor for pancreatic cancer independent of a specific drug effect yet warrants further investigation.

753. Insulin Glargine and Breast Cancer Risk: Comparison of Different Exposure Definitions

Paul JHL Peeters,[1] Marloes T Bazelier,[1] Tjeerd P Van Staa,[2] Anssi Auvinen,[3] Hubert GM Leufkens,[1] Frank de Vries,[1,4] Marie L De Bruin.[1] *[1]Utrecht Institute of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester, Manchester, UK; [3]School of Health Sciences, University of Tampere, Tampere, Finland; [4]Medical Center Maastricht and School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands.*

Background: Observational cohort studies have reported contradictory risk estimates for the association between insulin glargine and breast cancer risk. At the same time, studies have used very different ways to define exposure.

Objectives: The aim of this study was to assess the effect of exposure definition on breast cancer risk effect estimates associated with glargine use in type 2 diabetic women.

Methods: We performed a cohort study (2002–2013) in CPRD among adult female new insulin users. Patients were followed up for breast cancer occurrence. We used four models to define exposure: time-fixed, by type of insulin prescribed at baseline (intention-to-treat, model 1); time-fixed, by type of insulin prescribed any time during follow-up (immortal time, model 2); time-varying ('ever' versus 'never use', model 3); and stratified by both exposure to other insulins at the start of glargine treatment and by cumulative glargine use (model 4). Cox proportional-hazards models were used to estimate adjusted hazard ratios (HR).

Results: Among 11 630 patients with 5-year median follow-up (total of 61 262 years), 162 breast cancer events occurred. No risk difference was found in the

intention-to-treat design (HR = 0.94, [0.67–1.33]; model 1). A non-significant risk decrease was observed in the immortal time design (model 2) for exclusive use of glargine (HR = 0.73 [0.44–1.20]) and use of both insulin types (HR = 0.91 [0.64–1.30]). In a time-varying model, the risk was similar between 'ever' and 'never use' of glargine (HR = 1.00 [0.72–1.37]; model 3). No association was found with cumulative exposure to glargine, even after >5 years (model 4). When stratified by years of past exposure to other insulins, a linear trend was observed (p-trend = 0.03; model 4). The risk was significantly increased among users with high past use of other insulins (>3 years) and cumulative use of glargine of 1–3 years (HR = 5.18, [1.61–16.64]; model 4).

Conclusions: Variations in exposure definition led to minimal fluctuations in risk estimate for breast cancer associated with glargine use. Only when past exposure to other insulins and current cumulative use of glargine were taken into account simultaneously; differences between treatment groups were observed.

754. The Long-term Use of Calcium Channel Blockers and the Risk of Breast Cancer

Laurent Azoulay,[1,2] Sara Soldera,[2] Hui Yin,[1] Nathaniel Bouganim.[2] *[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; [2]Department of Oncology, McGill University, Montreal, QC, Canada.*

Background: The association between calcium channel blockers (CCBs) and the risk of breast cancer is controversial, with observational studies reporting conflicting results.

Objectives: The objectives of this population-based study were to determine whether the use of CCBs is associated with an increased risk of breast cancer overall and to assess whether this risk varies with cumulative duration of use.

Methods: A cohort of women newly treated with antihypertensive drugs between 1 January 1995 and 31 December 2009, followed until 31 December 2010, was identified using the UK Clinical Practice Research Datalink. CCB use was treated as a time-varying variable, with exposure lagged by 1 year for latency considerations and to minimize reverse causality. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of incident breast cancer associated with the use of CCBs, when compared with other antihypertensive drugs. A secondary analysis was conducted to assess whether the risk varied with cumulative duration of use (<5 years, 5–10 years, ≥10 years). All models were adjusted for a number of potential confounders, including age, smoking status, body mass index, excessive alcohol use, previous use of hormone replacement therapy, and various other prescription drugs.

Results: The cohort included 273 152 women. During 1 567 104 person-years of follow-up, 4520 women were newly diagnosed with breast cancer (incidence rate: 2.9 per 1000 per year). Compared with the use of other antihypertensive drugs, the use of CCBs was not associated with an increased risk of breast cancer (2.8 vs. 3.1 per 1000 per year, respectively; HR: 0.98, 95%CI: 0.92–1.04). In a secondary analysis, the risk did not vary according to cumulative duration of use (<5 years, HR: 0.97, 95%: 0.90–1.03; 5–10 years, HR: 1.08, 95%CI: 0.94–1.25; ≥10 years, HR: 0.69, 95%CI: 0.36–1.33).

Conclusions: The results of this large population-based study indicate that long-term use of CCBs is not associated with an increased risk of breast cancer among women newly treated with antihypertensive drugs.

755. Statin Use and Risk of Primary Liver Cancer in the UK Clinical Practice Research Datalink (CPRD)

Katherine A McGlynn,[1] Katrina Wilcox Hagberg,[2] Jie Chen,[1] Barry I Graubard,[1] W Thomas London,[3,4] Susan S Jick,[2] Vikrant V Sahasrabuddhe.[1] *[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA; [2]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, USA; [3]Fox Chase Center, Philadelphia, PA, USA; [4]Hepatitis B Foundation, Doylestown, PA, USA.*

Background: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely prescribed to reduce cholesterol levels. Studies have suggested that statins are associated with reduced risk of liver cancer, but much of the evidence is from regions of the world with high liver cancer incidence rates.

Objectives: The objectives of this study were to examine the association between statins and liver cancer

and to assess the effects of pre-existing liver disease and diabetes, two strong risk factors for liver cancer.

Methods: A nested case–control study was conducted within the United Kingdom's Clinical Practice Research Datalink (CPRD). Persons diagnosed with incident primary liver cancer between 1988 and 2011 were matched to up to four controls on age (same year of birth), sex, general practice, index date (1 year prior to case's diagnosis date), and number of years in the CPRD prior to the index date. We conducted additional analyses, further matching controls to cases on liver disease and, separately, diabetes status, to assess effect modification in persons at elevated risk for liver cancer. Adjusted odds ratios (ORadj) and 95% confidence intervals (95%CI) for associations of statins with liver cancer were estimated using conditional logistic regression adjusted for BMI, smoking, alcohol-related disorders, hepatitis B or C, diabetes, rare metabolic disorders, and use of paracetamol, aspirin, and antidiabetic medications.

Results: In total, 1195 persons with primary liver cancer were matched to 4640 controls. Statin use was associated with a significantly reduced risk of liver cancer (ORadj = 0.55, 95%CI 0.45–0.69), with a significant dose–response ($p < 0.0001$). This reduction in risk was significant in the presence (ORadj = 0.32, 95%CI 0.17–0.57) and absence of liver disease (ORadj = 0.65, 95%CI 0.52–0.81) and in the presence (ORadj = 0.30, 95%CI 0.21–0.42) and absence of diabetes (ORadj = 0.66, 95%CI 0.51–0.85).

Conclusions: In this study, statin use was associated with a significantly reduced risk of liver cancer. Risk was particularly reduced among persons with liver disease and persons with diabetes, suggesting that statin use may be especially beneficial in persons at highest risk of liver cancer.

756. When Do Regulatory Agencies Request Post-approval Registries for New Medicines? A Retrospective Review of Centrally Approved Products in Europe

Carla J Jonker,[1,2] Marijke HM van den Berg,[2] Arno W Hoes,[2] Peter GM Mol.[1,3] *[1]Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands.*

Background: At time of marketing approval, the knowledge of the benefits and risks of new medicines is not complete. When uncertainties remain, regulators and industry may agree on setting up drug or disease registries, in addition or as a substitute for further clinical trials. However, little is known on how often and why (for efficacy and/or safety concerns) these registries are requested and the determinants of such request.

Objectives: The aim of this study was to investigate for what purposes registries were requested for new medicines approved in Europe.

Methods: New medicines—new active substances including biosimilars—approved between 1 January 2007 and 1 January 2011 were identified from the European Medicines Agency website. European Public Assessment Reports (including Risk Management Plan specifications) were reviewed for the presence of a registry. The goal of registries was determined and key characteristics of medicines (drug class, type of molecule, level of innovation [classified as important, moderate, modest, and mere pharmacological/technological innovations], and size of safety population) and the regulatory procedure (orphan application, exceptional circumstances, or conditional approval; [y/n]). Multivariate logistic regression was applied to identify independent determinants of registry requests.

Results: For 41 (35%) of 116 new medicines approved, one or more registry studies were identified: 28 to address safety concerns, 23 to assess impact on pregnancy outcome, and 5 to address efficacy. Determinants associated with a registry request in univariate analyses were drug class (systemic anti-infectives HR 3.11 (95%CI: 1.06; 9.11)) and level of innovation (important drug innovations HR 16 (95%CI: 1.77;147)). Only important drug innovations HR 11.4 (95%CI: 1.17;110) remained a significant determinant in the multivariate analyses.

Conclusions: Registry studies are requested for a third of medicines approved in Europe, addressing primarily safety concerns as identified in the RMP. Medicines considered important innovations were more likely to have a registry possibly to obtain these medicines available to patients despite remaining uncertainties.

757. Awareness of Medication Safety Warnings: Results from a Survey of Patients and Caregivers in the USA

S Narayanan,[1] NL Rucker,[2] WR Bullman,[3] GC Alexander,[4] P Rausch.[5] *[1]Evidence Generation, Value and Access COE, Ipsos Healthcare, Washington, DC, USA; [2]Enhance Value, Bethesda, MD, USA; [3]NCPIE, Rockville, MD, USA; [4]Center for Drug Safety and Effectiveness, Johns Hopkins University, Baltimore, MD, USA; [5]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA.*

Background: Assessing receipt, understanding, and using of medication risk and drug safety alerts among patients (pts) and caregivers (CGs) could strengthen the development and dissemination of medication-related risk and safety information to the general public.

Objectives: The aim of this study was to conduct a national survey of pts/CGs to assess their knowledge, attitudes, and actions related to medication risk and safety information.

Methods: A cross-sectional online survey of pts and CGs was conducted (FDA grant no. 5U18FD004653) in November–December 2013 using a consumer panel in the USA. A geographically diverse sample of pts/CGs taking prescription medication(s) daily in the past 6 months to manage ≥1 chronic disease condition or who had a primary responsibility for helping another adult taking prescription medication was recruited. Survey collected demographics, clinical characteristics, medication-taking behavior, information-seeking behavior, and personal experience with and receipt of medication warnings/safety information. Descriptive statistics are reported.

Results: Two thousand consumers (1600 pts/400 CGs) completed the survey; age: 18–35 years: 28%, 36–49 years: 24%, 50–64 years: 33%, and 65+ years: 16%; female: 62%; education: ≤high school diploma/GED: 21%, vocational/technical school diploma/some college: 31%, ≥college associate degree: 47%; individuals with one, two, three, four, and greater than five chronic diseases was 21%, 22%, 20%, 16%, and 21%, respectively, and they took an average of 2.5, 3.7, 4.6, 6.4, and 8.5 prescription medications, respectively. Most common sources for medication risk/safety information were as follows: healthcare professionals (HCPs; 73%), Internet (59%), and pharmacists (55%). Approximately 62% were not aware of any safety warnings about their medications, 69% were not informed by their HCP of a potential severe/serious side effect of their medication, and among these, 10% actually experienced a serious drug reaction.

Conclusions: A significant proportion of survey respondents were not aware of or informed about their medication safety warnings. Modalities to improve communication (to pts/CGs) about medication risk/safety warrants scrutiny.

758. Perceptions about Medication Safety Warnings and Communication with Patients: Results from a Survey of Healthcare Providers in the USA

S Narayanan,[1] NL Rucker,[2] GC Alexander,[3] WR Bullman,[4] P Rausch.[5] *[1]Evidence Generation, Value and Access COE, Ipsos Healthcare, Washington, DC, USA; [2]Enhance Value, Bethesda, MD, USA; [3]Center for Drug Safety and Effectiveness, Johns Hopkins University, Baltimore, MD, USA; [4]NCPIE, Rockville, MD, USA; [5]Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA.*

Background: Effective communication of medication risk/safety by healthcare providers (HCPs) to their patients (pts) is critical to the pt understanding of medication risk/safety. Understanding HCP perceptions and their current communication practices could enable development of educational materials to improve communication on medication risk/safety.

Objectives: The aim of this study was to conduct a national survey of HCPs to assess their perceptions and actions related to communication of medication risk/safety information to their pts.

Methods: A cross-sectional online survey of HCPs was conducted (FDA grant no. 5U18FD004653) in November–December 2013 using an HCP panel in the USA. A geographically diverse sample of HCPs (primary care physicians (PCPs), pharmacists, nurse practitioners (NPs), and physician assistants (PAs)) spending ≥50% of time in direct ambulatory pt care (PCP/PA/NP) or working in a retail pharmacy (pharmacists), with ≥2 years of practice experience and seeing/consulting ≥20 pts/week were recruited. Survey collected practice characteristics, beliefs about medication risks, information-seeking behavior (self and that of pts), and communication on medication risk/safety.

Results: Eight hundred HCPs (200 each of PCPs/NPs/PAs/Pharmacists) participated. FDA-approved product

label (66%), journal articles/CME/Compendia (64%), and internet (57%) were top three sources to receive or learn about medication safety often/always. Majority (54%) believed their pts do not fully understand potential medication risks; 38% reported pts rarely ask questions about their medications, and 52%/51%/37% believed pts obtain 'medication risk/safety information' mostly from pharmacists/Internet/PCPs; only 31% of PCPs believed that pts obtain information from them; and 57%/52%/44%/39% of PCPs/pharmacists/NP/PA noted insufficient time as primary barrier to pt counseling on medication risks.

Conclusions: PCPs did not identify themselves as primary information source for medication risks; HCPs (especially PCPs/pharmacists) noted insufficient time for counseling. Ways to foster HCP-pt communication on medication risk/safety warrants scrutiny.

759. Online Physician Communities Offer Pragmatic Approach to Surveys Assessing Change in Knowledge as Part of Pharmacovigilance and Risk Minimization Plans

Alexander Liede,[1] Pamela M Peters,[2] J Michael Sprafka.[3] *[1]Center for Observational Research, Amgen, South San Francisco, CA, USA; [2]Medscape Education, New York, NY, USA; [3]Center for Observational Research, Amgen, Thousand Oaks, CA, USA.*

Background: Physician knowledge surveys are increasingly requested by drug manufacturers in the post-authorization setting as part of risk minimization plans. However, surveys alone do not ensure safe use of medicinal products. Surveys typically provide an estimate of knowledge at one point in time after drug approval. Limited guidance has been provided to manufacturers on how best to ensure external validity or maximize response rates or what constitutes acceptable knowledge. Online physician communities offer a pragmatic approach to maximizing response rates and assessing change in knowledge of drug safety risks by pairing educational programs with survey administration.

Objectives: The aim of this study was to measure knowledge and demonstrate knowledge acquisition after a learning activity administered to an online physician community.

Methods: Working with Medscape, a community of >2 million physicians worldwide, we developed an online educational program to measure knowledge using pre-intervention and post-intervention assessments. Independent experts developed survey questions and educational content related to denosumab and events of special interest. Eligible physicians were practicing oncologists treating ≥5 patients with bone metastases in the past 3 months.

Results: For the learning activity, four multiple choice questions were developed, and 264 US oncologists contributed pre/post data. Pre-education versus post-education, 74% vs 94% of oncologists, respectively, had three to four correct answers. An additional 1605 physicians from European countries also completed the learning activity. Overall, there was an increase in knowledge of 15.8%.

Conclusions: Online communities or professional societies offer a practical approach for the recruitment of physicians for knowledge surveys. The strategy extends beyond achieving good response rates representative of today's physicians who seek information online. The reduced effort and time demands to achieve results, the option to continually monitor responses over time, and the opportunity to demonstrate knowledge acquisition with online educational content offer clear advantages over traditional REMS protocols.

760. After a Decade of Risk Communication on Diabetes Risks Associated with Antipsychotic Drugs: Where Do We Stand on Prescriber Attitudes and Behaviors?

Elaine H Morrato,[1] Elizabeth Campagna,[2] Sarah Brewer,[2] Miriam Dickinson,[2] Deborah SK Thomas,[3] Richard C Lindrooth.[1] *[1]Colorado School of Public Health, Aurora, CO, USA; [2]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [3]University of Colorado Denver, Aurora Campus, Denver, CO, USA.*

Background: Patients taking antipsychotics are at increased risk for developing diabetes. Risk communication has advocated glucose testing with the greatest intensity of messaging targeting mental health providers, who treat 60% of adults prescribed antipsychotics in US Medicaid.

Objectives: The aim of this study was to assess risk knowledge, screening attitudes, and glucose testing intent at antipsychotic drug initiation and at annual follow-up.

Methods: All providers who prescribed antipsychotics in the Missouri Medicaid system ($N = 52\,620$ patients in 2011) were surveyed by mail. Responses were compared by physician specialty (Pearson's chi-square) for 924 survey respondents who treated adults. Multivariable log-binomial regression evaluated physician, practice, and patient factors associated with testing attitudes and intent.

Results: Mental health providers practicing in state Community Mental Health Centers (CMHCs) were more likely to report they would definitely order baseline testing than primary care (PCP) or other providers (56.6% vs. 39.1% and 23.5% respectively, $p < 0.001$) and were more likely to definitely order follow-up testing than private-practice psychiatrists (78.3% vs. 61.0%, $p < 0.01$). Mental health providers (regardless of setting) were greater promoters of screening adults taking antipsychotics with colleagues than PCP or other providers (61.8–76.2% vs. 32.8–49.4%, $p < 0.001$). In adjusted analysis, PCPs were 36% more likely to strongly agree that their practice was responsible for screening than CMHC providers ($p < 0.01$) but 42% less likely to strongly agree that adults starting antipsychotics needed screening ($p < 0.01$). The strongest predictor of screening intent was strongly disagreeing that "metabolic screening is not a priority for my organization" (94% more likely to screen at baseline, $p < 0.01$, and 74% more likely to screen annually, $p < 0.01$).

Conclusions: Significant disparities in diabetes screening intent and attitudes were found between prescriber specialties. Establishing organizational priority across all treatment settings will be important for achieving population-based risk minimization screening goals.

761. Assessment of YouTube Videos as a Source of Information on Medication Use in Pregnancy

Craig Hansen,[1] Julia D Interrante,[1] Elizabeth C Ailes,[1] Meghan T Frey,[1] Cheryl S Broussard,[1] Valerie J Godoshian,[1] Courtney Lewis,[1] Kara N Polen,[1] Kara N Polen,[1] Amanda P Garcia,[1] Suzanne M Gilboa.[1] *[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA.*

Background: Many women consult the Internet when making decisions around medication use in pregnancy.

Objectives: Our aim was to assess the content of videos discussing medication use in pregnancy that are publicly accessible on YouTube.

Methods: Using a combination of 289 medication terms and seven pregnancy-related terms, 2023 distinct paired search terms related to medications and pregnancy were used to extract metadata from the YouTube Application Programming Interface in June 2014. After excluding videos that did not have at least one medication and one pregnancy-related term in the title, we viewed and recorded additional information about each video, including the source of the video and any medications and associated adverse outcomes mentioned. For selected medications, we compared the Teratogen Information System (TERIS) ratings with the assessments of safety reported in the videos.

Results: Of the 651 videos with at least one medication and one pregnancy-related search term in the title, 314 had relevant information about medication use in pregnancy and were included in the analyses. The majority of videos were legal in origin (210/314; 67%). Antidepressants were the most common medication type mentioned (249/314; 79% of videos); 225 of these videos mentioned risks associated with selective serotonin reuptake inhibitors (SSRIs). In 88% of those videos (198/225), the SSRI was noted as unsafe; in contrast, the TERIS risk ratings for SSRIs range from "unlikely" to pose a teratogenic risk to "minimal" risk.

Conclusions: To our knowledge, this is the first assessment of the content of YouTube videos about medication use in pregnancy. For selected medications, such as SSRIs, the current YouTube video content does not adequately reflect what is known about the safety of their use in pregnancy. Given the high utilization of the Internet for health information, YouTube could serve as a valuable platform for communicating evidence-based medication safety information.

762. Determining Proton Pump Inhibitor Prescription Dispensing Patterns for Nova Scotia Seniors Pharmacare Program Beneficiaries

Jillian H Carter,[1] Ingrid Sketris,[2] Hala Tamim,[1] Adrian Levy,[1] Joanne Langley.[3] *[1]Community Health and Epidemiology, Dalhousie University, Halifax, NS, Canada; [2]College of Pharmacy, Dalhousie University, Halifax, NS, Canada; [3]Department of Pediatrics, Dalhousie University, Halifax, NS, Canada.*

Background: Proton pump inhibitors (PPIs) are frequently prescribed and often potentially inappropriately. The screening tool for older people's potentially inappropriate prescriptions (STOPP) for therapeutic dose PPIs has been adapted to examine the discontinuation, dose reduction, or switch to H2 receptor agonist (H2RA) at 60 days.

Objectives: Objectives of the present study were to (1) determine the PPI dispensing patterns at 60 days after initial dispensing for Nova Scotia Seniors' Pharmacare (NSSPP) beneficiaries newly dispensed PPIs, and (2) assess patients' predictors for continued dispensing of PPIs 60 days after being newly dispensed a high-dose PPI.

Methods: Our retrospective cohort study included beneficiaries of the NSSPP ages 66 years or older newly dispensed PPIs from 1 January 1996 to 31 March 2011. Patients excluded had risk factors that may require long-term PPI use such as cancer, NSAID use, or a recent gastrointestinal bleed. The main outcome measure was adherence to the adapted STOPP criteria. Descriptive statistics and logistic regression analysis were performed.

Results: 14 453 participants were included: 89.8% beginning on low dose and 10.2% beginning on high-dose PPI. Of those beginning on low PPI dose, 1.6% switched to high dose, and 40.9% stayed on low dose at 60 days. Of those beginning on high PPI dose, 10.3% switched to low dose, and 26.4% stayed on high dose at 60 days. Multivariate logistic regression analysis showed that for patients who were dispensed a high-dose PPI at baseline, NSSPP beneficiaries ≥86 years of age were significantly at increased odds to be dispensed PPI (low or high dose) at 60 days, compared with patients 66–75 years of age. There was also a significant increase for PPI dispensing at 60 days for patients residing in rural areas and those hospitalized the year before baseline PPI dispensing.

Conclusions: Many PPI prescriptions dispensed for NSSPP beneficiaries fail to adhere to the STOPP criteria. Three risk factors for failure to adhere to the STOPP criteria for patients prescribed high-dose PPI were identified: patient age ≥86 years, rural residency, and hospitalization at the time of cohort entry.

763. Prevalence of and Risk for Gastrointestinal Bleeding and Peptic Ulcerative Disorders in a Cohort of HIV Patients from a US Healthcare Claims Database

Vani Vannappagari, Nana Koram, Monica Kobayashi, Emily Bratton.

Epidemiology and Real World Evidence, ViiV Healthcare Limited, Research Triangle Park, NC, USA;

Department of Epidemiology, University of North Carolina -CH, Chapel Hill, NC, USA;

Epidemiology, GlaxoSmithKline, Research Triangle Park, NC, USA.

Background: GI bleeding and PUD among HIV patients are associated with increased morbidity and mortality.

Objectives: The aim of this study was to estimate frequency of and risk for GI bleeding and PUD in HIV-positive patients compared with age-and-gender-matched HIV-negative patients.

Methods: Using de-identified data from US healthcare claims database for the period from 1 January 2005 through 31 March 2013, cases of any GI bleeding and PUD among HIV patients were identified. Patients were included if they were ≥18 years and continuously enrolled for ≥6 months, with full pharmacy benefits and had a diagnosis of HIV (ICD9 042, V08). Participants with enrolment gap of ≥1 month were excluded. Among patients with multiple occurrences of GI bleeding or PUD, only the first diagnosis of the event (for HIV patients, after first record of antiretroviral therapy [ART]) was considered.

Results: Among the 88 920 HIV-infected patients, 9% had a GI bleeding event, 1% experienced an upper GI bleed, 6% experienced a lower GI bleed, 2% had a PUD diagnosis, and 0.6% had both GI/PUD within 31 days of each other. Among the 266 760 HIV-negative patients, respective frequencies were 6%, 0.6%, 4%, 1%, and 0.4% and were significantly different from HIV-positive patients ($p < 0.0001$ for each diagnosis subcategory). Among HIV patients with ART information and any GI/PUD event, the prevalence that used ART within 1 month of the outcome ranged between 80% and 82% (89–93% used ART within 3 months). The three most frequent medications used were Truvada, Atripila, and Norvir across all outcomes, although not ranked in that order for each subtype of GI/PUD. Presence of any comorbidity/coinfection and at least one co-medication were both significantly higher in HIV subjects compared with controls ($p < 0.0001$). Out of 8825 HIV patients with GI/PUD events, 2258 had at least one of the following: alcoholism, HCV, HBV, cirrhosis, *Helicobacter pylori*, or other bleeding disorder.

Conclusions: In this population, prevalence of GI bleeding was 10% and prevalence of 2% for PUD. HIV-infected subjects had higher frequencies of GI/PUD events and comorbidities/coinfections and co-medications than controls.

764. Acid Suppression Medications and Bacterial Gastroenteritis: A Population-Based Cohort Study

Li Wei,[1] Lasantha Ratnayake,[2] Gabby Phillips,[3] Chris C McGuigan,[3] Steve V Morant,[4] Robert W Flynn,[5] Isla S Mackenzie,[5] Thomas M MacDonald.[5] *[1]UCL School of Pharmacy, University College London, London, United Kingdom; [2]Medical Microbiology, James Paget University Hospitals NHS Foundation Trust, Great Yarmouth, Norfolk, United Kingdom; [3]Directorate of Public Health, NHS Tayside, Dundee, United Kingdom; [4]Medicines Monitoring Unit, Ninewells Hospital & Medical School, Dundee, United Kingdom.*

Background: Acid suppression medications are increasingly prescribed in both the community and hospital settings in the UK. However, these medicines have been implicated as a risk factor for bacterial gastroenteritis. Meta-analyses have provided inconsistent results about the association.

Objectives: To investigate whether acid suppression medicines increase the risk of bacterial gastroenteritis.

Methods: This was a cohort study linking prescribing data and microbiology stool sample results in Tayside, Scotland. Patients who received at least one dispensed prescription of acid suppression medicines between 1999 and 2013, and a propensity matched cohort, were included in the study. Studied were 564 969 patients: 188 323 exposed to acid suppression medicines (proton pump inhibitors and H2 receptor antagonists) and 376 646 in the control group. The outcome was a stool test that was positive for *Clostridium difficile*, *Campylobacter*, *Salmonella*, *Shigella* or *Escherichia coli O15*. The association between acid suppression medicines and risk of bacterial gastroenteritis was assessed by a Cox regression model.

Results: There were 149 636 incident stool tests of which 22 705 tested positive for one or more of five bacterial causes of gastroenteritis and 139 505 were negative. The positive results were 15 273 *C. difficile* (toxin positive), 6590 *Campylobacter*, 852 *Salmonella*, 129 *Shigella* and 193 *E. coli O157* with a total of 5 729 743 person-years follow-up time. The adjusted hazard ratios for tested positive diarrhoea for the proton pump inhibitor and H2 receptor antagonists exposed versus unexposed cohort was 2.72 (95% confidence interval 2.33, 3.17) during follow-up time in the community and 1.28 (1.08, 1.52) in hospitals. Compared with the unexposed cohort, patients in the exposed group had an increased risk of *C. difficile* and *Campylobacter* (adjusted hazard ratios of 1.70 (1.28, 2.25), 3.71 (3.04, 4.53) in the community, and 1.42 (1.17, 1.71), 4.53 (1.75, 11.8) in the hospitals, respectively).

Conclusions: The results suggest that community prescribed acid suppression medicines were associated with increased rates of positive stool samples for *C. difficile* and *Campylobacter* submitted from both the community and hospitals.

765. Risk of Upper Gastrointestinal Bleeding and Ulcers in Persons With Schizophrenia: A Danish Cohort Study

Cary Cotton[1], Dora F Farkas,[2] Nadia Foskett,[3] Henrik T Sørensen,[2] Vera Ehrenstein.[2] *[1]Center for Gastrointestinal Biology and Disease, University of North Carolina, Chapel Hill, NC, United States; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Roche Products Limited, Welwyn Garden City, United Kingdom.*

Background: Patients with schizophrenia have reduced life expectancy mediated in part by physical illness, including digestive diseases. The association between schizophrenia and nonvariceal upper gastrointestinal bleeding (UGIB), bleeding or non-bleeding gastroduodenal ulcers, has not been investigated.

Objectives: We examined the association of schizophrenia with three outcomes, UGIB, bleeding gastroduodenal ulcers, and non-bleeding gastroduodenal ulcers, and explored risk factors for UGIB and ulcers among schizophrenia patients.

Methods: We conducted a nationwide cohort study of all patients diagnosed with schizophrenia during 1980–2011 in Denmark, followed through 2012. We computed age- and sex-direct-standardized incidence rates and standardized incidence ratios of the outcomes among patients with schizophrenia compared with the general Danish population. We also examined somatic comorbidities and co-medications as risk

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factors for the three outcomes among patients with schizophrenia, treating them as time-varying variables.

Results: Among 39 359 newly diagnosed schizophrenia patients, we observed 1264 cases of UGIB, 459 cases of bleeding gastroduodenal ulcers, and 808 cases of non-bleeding gastroduodenal ulcers. Standardized incidence rates in patients with schizophrenia per 100 000 person-years were 401 (95% confidence interval (CI): 366–443) for UGIB, 163 (95% CI: 142–189) for bleeding gastroduodenal ulcers, and 249 (95% CI: 223–279) for non-bleeding gastroduodenal ulcers. The overall standardized incidence ratios were 2.9 (95% CI: 2.8–3.1) for UGIB, 2.4 (95% CI: 2.2–2.6) for bleeding ulcers, and 2.0 (95% CI: 1.9–2.2) for non-bleeding ulcers. Risk factors for the outcomes included advanced age at schizophrenia diagnosis, somatic comorbidity, and use of antithrombotic, antiplatelet, or anticonvulsant medications.

Conclusions: Patients with schizophrenia have approximately three times the risk of UGIB and twice the risk of bleeding and non-bleeding ulcers compared with the general population. Risk factors for UGIB and gastroduodenal ulcers among patients with schizophrenia are similar to those among the general population.

766. Risk of Acute Liver Failure in Patients With Drug-Induced Hepatitis: Evaluation of Hy's Law and a Novel Prognostic Model

Vincent Lo Re,[1] Kevin Haynes,[1] Kimberly A Forde,[1] David S Goldberg,[1] James D Lewis,[1] Dena M Carbonari,[1] Kimberly BF Leidl,[1] Rajender Reddy,[1] Melissa S Nezamzadeh,[1] Jason Roy,[1] Daohang Sha,[1] Amy R Marks,[2] Jolanda De Boer,[2] Jennifer L Schneider,[2] Brian L Strom,[3] Douglas A Corley.[2] *[1]Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [2]Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States; [3]Rutgers Biomedical & Health Sciences, Rutgers, the State University of New Jersey, Newark, NJ, United States.*

Background: Despite the clinical impact of hepatotoxicity, few studies have evaluated the ability of laboratory tests to predict risk of acute liver failure (ALF) among drug-induced hepatitis patients.

Objectives: We developed a novel prognostic model that identified drug-induced hepatitis patients at increased risk of ALF with high sensitivity and contrasted its performance with that of Hy's law (alanine or aspartate aminotransferase ≥3 times upper limit of normal [ULN] and total bilirubin ≥2 times ULN), the most commonly used algorithm to assess the severity of hepatotoxicity within the clinical trials setting.

Methods: We conducted a retrospective cohort study among 5 484 224 Kaiser Permanente Northern California members between 2004 and 2010. Within this population, 15 353 members without pre-existing liver disease received a drug-induced hepatitis diagnosis and had liver aminotransferase levels above ULN. Thirty ALF events were confirmed by medical record review. Logistic regression was used to develop prognostic models for ALF comprised of laboratory results measured on the date of the drug-induced hepatitis diagnosis.

Results: Hy's law biochemical criteria had high specificity (0.92) and negative predictive value (0.99), but low sensitivity (0.68) and positive predictive value (0.02), for incident ALF. A prognostic model comprised of platelet count and total bilirubin had high discrimination for ALF (*c*-statistic, 0.87 [95% confidence interval, CI, 0.76–0.96]) and enabled calculation of a risk score (drug-induced liver toxicity [DrILTox] ALF score). A cut-off identifying high-risk patients had a sensitivity of 0.91 (95% CI, 0.71–0.99) and specificity of 0.76 (95% CI, 0.75–0.77).

Conclusions: Hy's law has low sensitivity, but high specificity, for ALF. The DrILTox ALF score, based on platelet count and total bilirubin, discriminated the risk of developing ALF among suspected drug-induced hepatitis patients with high sensitivity. Future studies should evaluate the classification performance of the DrILTox ALF score in other populations and determine if its use improves outcomes.

767. Validation of a Coding Algorithm for Intra-Abdominal Surgeries and Adhesion-Related Complications in an Electronic Medical Records Database

Frank I Scott,[1,2] Ronac Mamtani,[3] Kevin Haynes,[2] David S Goldberg,[1,2] Najjia N Mahmoud,[4] James D Lewis.[1,2] *[1]Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [2]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia,*

PA, United States; [3]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, United States; [4]Department of Surgery, University of Pennsylvania, Philadelphia, PA, United States.

Background: Adhesion-related complications following intra-abdominal surgery result in significant morbidity and mortality. Epidemiological data on risk factors for adhesion-related complications are limited in part by the lack of population-based data with both validated surgical procedures and adhesion-related outcomes such as small bowel obstruction (SBO) or need for lysis of adhesions.

Objectives: To assess the accuracy of diagnostic codes for surgeries and adhesion-related complications within The Health Improvement Network (THIN).

Methods: Individuals >18 years old within THIN with >1 year of follow-up prior to an incident intra-abdominal surgery and subsequent SBO or lysis of adhesions were identified using diagnostic and procedure codes. To compute positive predictive values (PPVs), surveys were sent to general practitioners from a stratified random sample of subjects for confirmation of the surgery, SBO, or adhesiolysis code. General practitioners were advised to provide documentation confirming these procedures and complications when available. Completeness of recording was estimated by comparing observed rates to expected rates of both surgical procedures and adhesion-related complications based on national and published data.

Results: Of 245 questionnaires, 217 (89%) were returned (180 SBO and 37 adhesiolysis). The PPV of codes for surgery was 94.5% (95% CI: 91–97%). Correctly coded were 88.8% (95% CI: 83–92%) of procedure types. The PPVs for SBO and adhesiolysis were 86.1% (95% CI: 80–91%) and 89.2% (95% CI: 75–97%), respectively. Colectomy, appendectomy, and cholecystectomy rates were 99%, 95%, and 84% of that in national United Kingdom data, respectively. Adhesion-related complication rates were similar to previously published data for colectomy (5.0% vs. 5.1%), appendectomy (0.9% vs. 1.0%), and small bowel surgeries (5.1% vs. 4.7%).

Conclusions: Surgical procedures, SBO, and adhesiolysis can be accurately identified within THIN using diagnostic codes. THIN represents a new tool for pharmacoepidemiology studies of medications as risk factors for adhesion-related complications.

768. Pharmacovigilance Knowledge and Practices Among Health Care Professionals; a Regional Survey

Maria Rizvi, Mehreen Abbas.

Medical Affairs, Pharmacovigilance & Clinical Research, Getz Pharma Pvt Ltd, Karachi, Pakistan.

Background: Underreporting of adverse drug reactions (ADRs) is the main obstacle in successful development of pharmacovigilance programs. Healthcare professionals (HCPs) possess major responsibility to report ADRs and strengthen pharmacovigilance program of their country.

Objectives: To assess the knowledge and practices of pharmacovigilance among HCPs constituting pharmacists, physicians, and nurses.

Methods: A cross-sectional survey was conducted at the 1st ISoP-UMC Training held in Philippines from 5 to 7 June 2014. Majority of participants belonged to the pharmaceutical industry and regulatory authorities of South and South East Asia. Out of 25 distributed forms, 21 were returned, and data were analyzed using SPSSv.20.

Results: Mean age of survey participants was 36.05 ± 9.75 years. Out of 21 participants, 20 (95.24%) responded to have regulations on ADR reporting in their respective countries. All 21 participants knew how to report ADRs, and 17 (80.95%) reported ADRs to their national pharmacovigilance centers. Twenty (95.24%) participants said that ADRs should not be reported for newly marketed drugs only. All agreed that pharmacovigilance adds value to their practices, quality of care, and benefit to patients; 15 (71.43%) believed to have a mandatory pharmacovigilance plan for all marketed products. Main reasons of discouragement in reporting ADRs were lack of reporting culture (43.75%), lack of awareness (25.0%), time constraints (15.63%), and unavailability of accurate information (15.63%).

Conclusions: Majority of HCPs are well aware of basic pharmacovigilance knowledge and practices and consider such initiatives beneficial for patients' health. However, they still have few reasons of discouragement in reporting ADRs that need to be addressed for advancement of the pharmacovigilance program.

769. Prospective Evaluation of vigiRank for First-Pass Screening in Real-World Signal Detection

Ola Caster,[1,2] Lovisa Sandberg,[1] Kristina Juhlin,[1] Sarah Watson,[1] G Niklas Norén.[1,3] [1]*Uppsala Monitoring Centre, Uppsala, Sweden;* [2]*Department of Computer and Systems Sciences, Stockholm University, Kista, Sweden;* [3]*Department of Mathematics, Stockholm University, Stockholm, Sweden.*

Background: vigiRank is a statistical signal detection method for pharmacovigilance. It accounts not only for the observed versus expected number of reports on a drug–adverse drug reaction (ADR) pair, but also for the quality, recency, content and geographical spread of its reporting. Previous evaluation against historical safety signals suggested that vigiRank outperforms disproportionality analysis, the current state-of-the-art.

Objectives: To evaluate vigiRank in prospective real-world signal detection by comparing its performance to that observed historically for disproportionality analysis.

Methods: During a period in the spring of 2014, vigiRank was used to identify drug–ADR pairs for initial manual assessment based on data from VigiBase®, the WHO global individual case safety reports database. The scope was restricted to WHO-ART critical terms and pairs reported by at least two countries. Unless kept under review, each pair was classified as either labelled, dismissible or a potential signal. All potential signals were then subjected to in-depth review, and 9 months later, the outcome was analysed. A comparison was made to historical metrics for signal detection with the same scope in VigiBase during the years 2009–2013, when first-pass screening relied on disproportionality analysis.

Results: Assessed were 311 drug–ADR pairs identified by vigiRank. Of these, 153 were labelled, 116 were dismissed, 15 were kept under review and 27 (8.7%) were classified as potential signals. The historical rate of potential signals for disproportionality-based signal detection was about the same, 300 of 3518 (8.5%). At the time of analysis, 24 of the 27 potential signals for vigiRank were decided upon: 5 were dismissed as non-signals, 9 were kept under review and 10 (42%) became actual signals. Hence, overall (at least) 10 of the initial 311 pairs (3.2%) identified by vigiRank ended up as signals, to be compared with 37 of 3518 (1.1%) historically for disproportionality-based signal detection ($p < 0.01$).

Conclusions: Combining multiple strength-of-evidence aspects as in vigiRank significantly outperforms disproportionality analysis alone in real-world pharmacovigilance signal detection.

770. Evaluation of EU Post-Authorization Safety Studies Using EU-RMP/European Public Assessment Reports: Analysis, Trends, and Implications

David Neasham,[1] Sarah Baradaran,[1] Corina Chalkiadaki,[1] Ravi Sadasivan,[1] Beth L Nordstrom,[1] Matthew W Reynolds.[1] [1]*Evidera, London, United Kingdom.*

Background: All medications seeking marketing authorization in the European Union need to submit a risk management plan outlining known risks and post-authorization studies (PAS) to monitor potential risks. However, information is limited on the trends and PAS requirements for medications seeking marketing authorization.

Objectives: To assess European Union PAS trends and requirements (number and types of PAS) from 2009 to 2014.

Methods: A review of all European public assessment reports accessible via the European Medicine Agency (EMA) website was conducted for 2009–2014. Data on the type of drug and type of PAS were identified and analyzed to assess PAS trends and requirements.

Results: In 2009–2014, 425 drugs were granted market authorization by the EMA. The proportion of approved drugs requiring PAS has steadily increased, from 39% in 2010 to 76% in 2014. Overall, 90% of biologics required PAS (in addition to routine pharmacovigilance activities) compared with 79% of small molecules. This difference has steadily decreased over the years (from 89% and 67% of biologics and small molecules, respectively, in 2009 to 100% and 81% in 2014). Among the drugs requiring at least one PAS, each biologic and small molecule required, on average, 3.4 and 4.1 PAS, respectively. Biologics (including biosimilars) required a higher number of PAS assessing drug safety and/or efficacy compared with small molecules (2.0 vs. 1.6 studies, $p < 0.05$). Small molecules required a higher number of PAS on drug utilization compared with biologics and biosimilars (0.4 and 0.1 studies, $p < 0.05$). In addition, the proportion of drugs requiring PAS was higher if it had an orphan indication, a conditional approval,

an approval under exceptional circumstances, or required additional monitoring compared with drugs without these indications or approvals.

Conclusions: The proportion of new approvals requiring PAS has increased since 2010. PAS requirements differed based on drug type and nature of the indication/approval. The trends highlight the increasing PAS requirements by the EMA and the need for adequate planning for PAS when seeking market authorization.

771. Comparison of Events in Spontaneous Adverse Event Reports to Events Discussed Within Context of Drug Use on Facebook and Twitter

Gregory Powell,[1] Heidi Bell,[2] Harold Rodriguez,[3] Michele Thomas,[4] Jeffery Painter,[1] Cath Harvey,[5] James Blowers,[1] Nabarun Dasgupta.[3] *[1]GlaxoSmithKline, RTP, NC, United States; [2]Zero Chaos, Raleigh, NC, United States; [3]Epidemico, Boston, MA, United States; [4]Blue Zone Industries, Chester Springs, PA, United States; [5]GlaxoSmithKline, London, United Kingdom.*

Background: Spontaneous data are the benchmark of post-marketing safety surveillance. Recently, there has been interest in exploring online social listening to supplement traditional pharmacovigilance data.

Objectives: To compare events from spontaneous adverse event reports with public Twitter and Facebook posts mentioning medication use.

Methods: All spontaneous adverse event reports received in the past 2 years by GlaxoSmithKline (GSK) were reviewed and MedDRA preferred terms (PTs) were counted. For social listening data, all publically available posts within the last 2 years on Facebook and Twitter that contained at least one prescription/OTC product and one event were collected and de-identified. Data vocabularies were standardized using a vernacular-to-MedDRA dictionary for medical conditions and a custom curated vernacular dictionary for drugs. All posts were analyzed, and PTs were counted.

Results: Overall, there were 682 036 individual PTs mentioned in spontaneous data compared with 15 650 108 PTs in Facebook and 6 441 679 in Twitter during the same time period. There were 8088 unique PTs in spontaneous data, 946 unique PTs in Facebook, and 702 unique PTs in Twitter. There were four PTs that were common in the top-10 list for all three data sources (headache, malaise, drug ineffective, and fatigue). Terms unique to spontaneous data top-10 list were product quality complaint, rash, nausea, vomiting, diarrhoea, and drug administration error. Terms unique to Facebook top-10 list were weight increased, skin discomfort, and infection. The term insomnia was unique to Twitter top-10 list.

Conclusions: Social listening data contain a significant number of discussions relating to events associated with drug/product use. There is some overlap between the three data sources with respect to the types and frequencies of events being discussed, although differences also exist. More research is needed to understand the benefits social listening data may offer to traditional pharmacovigilance.

772. Bias in Spontaneous Reporting of Adverse Drug Reactions in Japan

Shinichi Matsuda,[1] Kotonari Aoki,[1] Takuya Kawamata,[1] Tetsuji Kimotsuki,[1] Takumi Kobayashi,[1] Hiroshi Kuriki,[2] Terumi Nakayama,[1] Seigo Okugawa,[1] Yoshihiko Sugimura,[1] Minami Tomita,[1] Yoichiro Takahashi.[1] *[1]Drug Safety Division, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan; [2]Clinical Development Division, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan.*

Background: Attitudes of healthcare professionals regarding spontaneous reporting of adverse drug reactions (ADRs) in Japan are not well known, and Japan's unique system of early post-marketing phase vigilance (EPPV) may affect these reporting attitudes.

Objectives: To describe potential effects of EPPV and to test whether ADR seriousness, prominence, and frequency are related to changes in reporting over time.

Methods: A manufacturer's database of spontaneous ADR reports was used to extract data from individual case safety reports for five drugs subjected to EPPV. The trend of reporting and the time lag between ADRs onset and reporting to the manufacturer were examined. The following indices for ADRs occurring with each drug were calculated and analyzed for reporting trend changes over time: serious : non-serious ratio, high prominence : low prominence ratio, and high frequency : low frequency ratio.

Results: For all five drugs, the time lag between ADRs onset and reporting to the manufacturer were shorter in

EPPV period than in post-EPPV period. All drugs showed higher serious : non-serious ratios in post-EPPV period. No specific patterns were observed for high prominence : low prominence ratio. The high frequency : low frequency ratio for peginterferon alpha-2a and sevelamer hydrochloride decreased steadily throughout the study period.

Conclusions: Healthcare professionals may be more likely to report serious ADRs than to report non-serious ADRs, but the effect of event prominence on reporting trends is still unclear. Factors associated with ADR reporting attitude in Japan might be different from those in other countries because of EPPV and the involvement of medical representatives in the spontaneous reporting process. Pharmacovigilance specialists should therefore be cautious when comparing data between different time periods or different countries. Further studies are needed to elucidate the underlying mechanism of spontaneous ADR reporting in Japan.

773. Experiences With a Computer-Assisted Database Screening Tool at the Netherlands Pharmacovigilance Centre Lareb

Florence van Hunsel,[1] Corine Ekhart[1]. [1]*Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, Netherlands.*

Background: The Netherlands Pharmacovigilance Centre Lareb uses two different methods for signal detection: a case-by-case method where all reports are individually assessed with the aim to detect potential signals. Because multiple assessors are involved in this process, a computer-assisted database screening tool is in place to minimize the risk for missing potential signals.

Objectives: To describe the experiences of using a screening tool as an additional method to case-by-case analysis in 2014.

Methods: Associations can be automatically selected by the screening tool based on one or more of the following pre-defined criteria: ATC code, adverse drug reaction being unlabeled in the SmPC, number of reports, lower limit of 95% confidence interval threshold of the reporting odds ratio and date set during previous analysis. Associations automatically selected by the screening tool undergo a short analysis by trained pharmacovigilance assessors. This short analysis can lead to alteration of pre-defined thresholds (for instance increasing the number of reports needed to automatically open the association) or selection for a more detailed analysis (typically 2–8 h duration). This detailed analyses are the basis of disseminated signals and publications. The number of short and detailed analyses based on the database screening tool is compared with analyses based on the case-by-case method.

Results: A total of 312 associations were automatically selected for a short analysis using the pre-defined criteria for screening. Of these, 13 were analysed in more detail.

A total of 108 detailed analyses were based on case-by-case analyses of 9123 reports. One association was simultaneously picked up with the screening algorithm and case-by-case analyses (paracetamol and metabolic acidosis).

Conclusions: The computer-assisted database screening tool cannot replace expert clinical reviewers doing case-by-case analyses. However, because the number of reports Lareb receives is growing quickly, a screening tool can be of aid in avoiding signals that are missed when confronted with large numbers of drug–adverse drug reaction combinations.

774. The Role of Registries in European Post-Marketing Surveillance: A Retrospective Analysis of Centrally Approved Products During 2005–2013

Jacoline Bouvy,[1] Xavier Kurz,[1] Kevin Blake,[1] Giampiero Mazzaglia,[1] Jim Slattery,[1] Corinne de Vries,[1] Marie L De Bruin,[2] Peter Arlett.[1] [1]*European Medicines Agency, London, United Kingdom;* [2]*Utrecht University, Utrecht, Netherlands.*

Background: At initial authorisation of new products, marketing authorisation holders may be requested to set up a registry in order to collect more data on the use of their product in everyday clinical use. However, the current approach to registries might not be the most efficient, and information regarding the frequency by which registries are requested, as well as how requirements regarding registries are fulfilled, have not been systematically collated.

Objectives: To assess the frequency and outcomes of registries that were required for centrally approved products (CAPs) authorised between 2005 and 2013.

Methods: A cohort of all CAPs for innovator products during 2005 (when risk management plans were introduced in Europe) until the end of 2013 was created.

We assessed whether a registry was specified as a legal obligation of the initial marketing authorisation. A registry was defined as an observational cohort study, collecting specified outcomes for a population defined by a particular disease, condition or exposure. We collected the following data for all products as well: indication; date of first market authorisation; whether an orphan medicine, conditional approval or approval under exceptional circumstances; current marketing status; and number of days the initial marketing application process took (in days).

For the CAPs with a registry, the following data regarding the registries were collected: intended start + end date; planned number of patients; number of sites + countries in registry; status of registry; has registry resulted in new safety/effectiveness data; was registry newly set up; and endpoints used (including endpoints relevant for health technology assessment).

Results: In total, 345 products were approved during 2005–2013. For 45 products (13%), a registry was requested as a specific obligation. As this study is still ongoing, no further results are available, but will be available by June 2015.

Conclusions: It is anticipated that the results of this study will be considered by the European Medicines Agency scientific committees to further inform them of the nature and outcomes of their requests for registries.

775. Framework for Impact Assessment of Regulatory Science: Application to the PROTECT Project

Xavier Kurz,[1] Peter Arlett,[1] Jim Slattery,[1] Kevin Blake,[1] Corinne de Vries.[1] *[1]European Medicines Agency, London, United Kingdom.*

Background:]Regulatory agencies are at the forefront of regulatory sciences aiming to improve evaluation of quality, efficacy and safety of medicinal products. These projects generate many outputs that are not immediately transferable into actual outcomes. The European Medicine Agency developed a framework for impact assessment to prioritise outputs for active implementation into regulatory practice. As a test case, it was applied to the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project (www.imi-protect.eu).

Objectives: To apply the framework for impact assessment on results of PROTECT to test its feasibility and draw lessons on its generalisibility**.**

Methods: The framework for impact assessment includes three domains (behaviour, process and outcome) and a semi-quantitative evaluation of outputs in terms of (1) potential impact of change on public health, (2) maturity, (3) feasibility (i.e. need for resources, acceptability and alignment with legislation) and (4) timing of implementation. All planned PROTECT deliverables were screened. Intermediate or illustrative outputs such as specific case studies were not further considered.

Results: Of 101 deliverables, 43 were selected and evaluated. They concern methods and methodological standards for pharmacoepidemiology and drug utilisation studies; guidance for signal detection; tools supporting pharmacovigilance; guidance for benefit–risk integration and representation; and patients' involvement in pharmacovigilance and benefit–risk assessment. Overall scores for public health impact and feasibility (incl. timing for implementation) were computed and tabulated and displayed graphically.

Conclusions: A structured framework for impact assessment of project outputs is useful to prioritise allocation of resources to support change in practice. At minimum, applying the framework will ensure that explicit prioritisation occurs. Graphical displays facilitate visualisation of overall potential impact of a project and comparison of different outputs within a project. Applying the approach to PROTECT identified those that may most readily be outcomes. Their implementation will further inform on the utility of the approach.

776. Impact of Scheduled Post-Marketing Safety Summary Analyses on Regulatory Actions

Shohko Sekine,[1] Ellen E Pinnow,[2] Rebecca Kurtzig,[2] Eileen Wu,[2] Hall Marni,[2] Gerald Dal Pan.[2] *[1]Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; [2]Office of Surveillance and Epidemiology, U.S. Food and Drug Administration, Silver Spring, MD, United States.*

Background: Pursuant to Section 915 of the Food and Drug Administration Amendments Act of 2007, FDA conducts scheduled summary analyses of the adverse drug reaction reports received for drugs and therapeutic biologics 18 months after approval or after 10 000 patients have used the product, whichever is later. The impact of these scheduled summary analyses on subsequent regulatory actions has not been studied.

Objectives: To characterize outcomes of the scheduled summary analyses and assess the value of these analyses in FDA's post-marketing safety program.

Methods: We used records from FDA's website and internal FDA records to obtain information on all drugs and therapeutic biologics approved between 27 September 2007 and 26 June 2013, including details of the marketing application history, marketing approval, post-marketing safety reviews, post-market safety-related regulatory actions, and the scheduled summary analyses. We included post-marketing drug safety regulatory actions taken from 27 September 2007 to 26 September 2014. Descriptive statistics were used to analyze the data. To evaluate the impact of these analyses, we describe the relationship between the results of the scheduled analyses and product characteristics such as novelty, therapeutic area, regulatory approval pathway, and other safety actions.

Results: Between 27 September 2007 and 26 June 2013, 488 NDAs and BLAs were approved. As of 12 February 2015, 280 scheduled analyses have been completed. Of the completed analyses, 69 were for new molecular entity drugs, 205 were for non-new molecular entity drugs, and six were for therapeutic biologics. Preliminary data show that 47 completed analyses generated 112 signals. The details of these signals, their impact on subsequent regulatory action, and their relationship to product characteristics will be presented at the ICPE meeting.

Conclusions: The final analysis of the data will characterize the impact of the scheduled analyses on detecting safety signals. This project will provide data on how to effectively and efficiently implement the scheduled analysis process.

777. Utility of Social Listening in Pharmacovigilance for Groups of Special Interest: Product Complaints, Pregnancy, Pediatric, and the Elderly

Heidi G Bell,[1] Laurie S Anderson,[1] Nancy A Yuen,[1] Bridget Ruane,[2] Harry Seifert,[2] Gregory E Powell.[1]
[1]Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Research Triangle Park, NC, United States; [2]Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Collegeville, PA, United States.

Background: There is interest in exploring social listening to supplement traditional pharmacovigilance methods.

Objectives: To assess the potential of social listening for augmenting current sources of data for subpopulations.

Methods: Publically available Facebook and Twitter posts for 1 year containing 15 GSK products (eight over-the-counter (OTC) and seven RX only (RX)) were de-identified. Data vocabularies were standardized using vernacular to MedDRA dictionary for medical conditions and custom curated vernacular dictionary for products. An automated algorithm categorized possible adverse events (proto-adverse events (proto-AEs)) or product mentions (MEN), and pharmacovigilance specialists reviewed these for accuracy of categorization, relevance to subpopulations of interest, and to characterize posts.

Results: Reviewed were 9853 posts (2496 proto-AEs and 7357 MEN). 398 (4%) were product complaints, 98 (0.9%) were related to pregnancy, 84 (0.9%) referenced pediatric patients, and 6 (0.06%) were in geriatric patients. For product complaints: 155 (39%) proto-AEs and 243 (61%) MEN. Breakdown by product type: 298 (75%) OTC and 100 (25%) RX. Most common complaints were formulation (177, 44%), cost (95, 24%), and advertisement (57, 14%). For pregnancy, breakdown by product type: 86 (88%) OTC and 12 (12%) RX; 18 (18%) were proto-AEs and 80 (82%) were MEN. Most frequent proto-AE was drug ineffective. Most frequent topics in MEN were benefit, indication, and safety. For pediatric patients: 11 (13%) were proto-AEs, most commonly drug ineffective and gastrointestinal effects. Numbers of geriatric patients were not large enough for further review.

Conclusions: For 15 GSK drugs, social media posts contained a number of discussions relating to product complaints, with fewer posts for pregnancy, pediatrics, and geriatrics. More research is needed to understand the incremental benefits social listening offers over traditional pharmacovigilance.

778. A Statistical Method for Estimating the Prevalence of Adverse Drug Reactions in Hospitalized Patients Using Laboratory Results from Electronic Health Records

Dukyong Yoon,[1,2] Man Young Park,[3] Eun Kyoung Ahn,[1] Soo Yeon Cho,[1] Dahye Shin,[1] Jihyun Kim,[1] Hojun Park,[1] George Hripcsak,[2,4] Rae Woong Park.[1,2]
[1]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Republic of Korea;

[2]*Observational Health Data Sciences and Informatics, New York, United States;* [3]*KM Health Technology Research Group, Korea Institute of Oriental Medicine, Daejeon, Republic of Korea;* [4]*Department of Biomedical Informatics, Columbia University Medical Center, New York, United States.*

Background: Adverse drug reactions (ADRs) are an important cause of iatrogenic morbidity and mortality in hospitalized patients. It is important to clarify the prevalence of ADRs when developing health-related policies. However, the existing rule-based methods have shown low detection rates and are limited in their generalizability to different hospitals.

Objectives: We aimed to develop a method to estimate the prevalence of ADRs based on statistical methods that can be generalizable across hospitals.

Methods: We evaluated the 1005 drugs prescribed and administered enterally or parenterally (except fluids) in the subject hospital to determine their odds ratios for 10 laboratory abnormalities associated with hepatic injury, renal injury, eosinophilia, thrombocytopenia, and altered bleeding time using electronic health records. Conditional logistic regression was used to analyze data of age-, gender-, admitting department-, and major diagnosis-matched exposed and non-exposed patients. After filtering out drug-abnormality pairs considered as confounding by indication, additionally occurred laboratory test abnormalities due to the drugs were calculated with odds ratios. We estimated the prevalence of ADRs by dividing additionally occurred abnormalities by the number of hospitalized patients in the subject hospital.

Results: ADRs were detected in 14.71 patients per 100 hospitalized patients (95% confidence interval (CI), 14.45–14.90). The rates according to type of ADR were as follows: 7.22 patients per 100 patients (95% CI, 7.05–7.36) for hepatic injury, 5.94 (95% CI, 5.82–6.03) for renal injury, 0.91 (95% CI, 0.86–0.95) for eosinophilia, 7.52 (95% CI, 7.41–7.65) for thrombocytopenia, and 4.53 (95% CI, 4.38–4.65) for altered bleeding time.

Conclusions: We were able to estimate the prevalence of ADRs using our method. The developed method can be generalized because it was based on general statistical methodology and epidemiological study design rather than on rules specific to each hospital. Thus, this approach can provide objective information that can be compared across hospitals.

779. Active Surveillance of Adverse Drug Reactions Using Administrative Databases

Ella T Nkhoma,[1] Kyna Gooden,[2] Jennifer Wood,[2] Brian Dreyfus,[1] Heather Mazakas,[3] Andres Gomez.[2] [1]*Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb, Wallingford, CT, United States;* [2]*Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb, Hopewell-Pennington, NJ, United States;* [3]*United Biosource Corporation, Blue Bell, PA, United States.*

Background: Spontaneous reporting systems for adverse drug reactions present many challenges including under-reporting, reporting bias, and an unknown underlying population at risk.

Objectives: To evaluate the use of administrative databases in detecting adverse drug reaction signals for active surveillance.

Methods: We investigated 55 drug–event pairs, including nine known signals, in three US insurance claims databases (two private and one Medicaid) and a UK electronic medical record database for the years 2008–2012. Signals were identified comparing the number of cases among patients prescribed the drug of interest to (1) all patients in the database, (2) self at 6 months prior to drug initiation (self-controlled method), and (3) patients prescribed a comparator drug/drug class. For all events, we defined different signaling rules based on the size of the effect estimate, the lower limit of the 95% confidence limit (CL), and the number of events for the drug of interest. The base definition was a lower limit of the 95% CL consistently >1. We computed performance metrics for each signaling rule, database, and comparison method, including sensitivity, specificity, false positive rate, and area under the curve. All analyses were conducted using SAEfetyWorks and SAS v9.2.

Results: Performance metrics varied across events, databases, and comparison methods. The self-controlled method had the lowest false positive rate when databases were examined individually. Applying the base definition to more than one database, the self-controlled method had the highest sensitivity (80%) and specificity (69%), with a false positive rate of 50%. The comparator drug/drug class method had the poorest sensitivity (0%) and a false positive rate of 80%. Across methods, the electronic medical record database had the best prediction with an area under the curve varying between 81% and 98.5% for the lower limit of the 95% CL.

Conclusions: The performance of each comparison method varied according to database. The self-controlled method performed consistently better than other methods in terms of sensitivity, specificity, and false positive rate.

780. The Impact of the New Pharmacovigilance Legislation on the Applications and Files Submitted to the Department of Adverse Drug Reactions of the National Organisation for Medicines in Greece (EOF)

Eirini Apostolidou,[1] George Aislaitner,[2] Leonidas Klironomos,[2] Agni Kapou,[2] Dimitrios Kouvelas.[1] *[1]Department of Pharmacology and Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; [2]National Organisation for Medicines (EOF), Athens, Greece.*

Background: The European Union (EU) pharmacovigilance legislation has undergone a major review. The new pharmacovigilance legislation came into effect across the European Union in July 2012 as the outcome of the changes introduced by Regulation (EU) No. 1235/2010 and Directive 2010/84/EU and was transposed in the Greek national legislation.

Objectives: To identify the impact of the new pharmacovigilance legislation on the applications and files submitted to the Department of Adverse Drug Reactions of the National Organisation for Medicines in Greece (EOF).

Methods: The relative Department of EOF keeps a record of all the types of submissions that will be assessed. These submissions are sorted and categorised according to their type and have been used to discuss the effects of the new pharmacovigilance legislation in EU.

Results: The number of risk management plans (RMPs) accompanied by educational material that are submitted to the National Organisation of Medicines in Greece has greatly increased. The number of Dear Health Care Professional Communications has also increased, along with the number of respective public communications/press releases. These changes are the result of the implementation of the new pharmacovigilance legislation. Criticism with respect to the role of RMPs and Dear Health Care Professional Communications has been raised.

Conclusions: The increasing number of submissions is an indication of efforts made towards increasing the quality and quantity of communication of risks to prescribers and the public and increased transparency for the overall risk assessment procedure. It is essential that a strengthened system of pharmacovigilance does not lead to expedited/premature granting of marketing authorizations. As part of the new EU pharmacovigilance legislation's scope, RMPs are not aimed to reassure the public on the safety of products, but to provide clear information regarding the safe use of products, so that prescribers and consumers are fully aware of any safety concerns.

781. Comparison of Safety Signal Detection Algorithms Used in Data Mining With Regard to Masking Bias

David J Nimke,[1] Vaishali K Patadia.[2] *[1]Global Pharmacovigilance, Astellas Pharma Global Development, Inc., Northbrook, IL, United States; [2]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: There is evidence that signal generation from disproportionality analyses could be suppressed by a marked increase in the frequency of reports among one or more drugs constituting the background, a bias termed *masking*. A comparison of signal detection algorithms with regard to differences in masking susceptibility has not been published to date.

Objectives: Characterize the magnitude and the extent to which masking persists for empirical Bayes geometric mean (EBGM), proportional reporting ratio (PRR) and reporting odds ratio (ROR) over time under a range of scenarios

Methods: The EBGM, PRR and ROR scores for every non-statin (e.g. aspirin) rhabdomyolysis drug–event pair in the Food and Drug Administration Adverse Event Reporting System was calculated from 1997 to 2013 in a cumulative way (e.g. 1997, 1997–98, 1997–99)($n = 28290$) using all other drugs as the background. The process was repeated using a background that excluded statin products. Masking was measured by dividing the score (e.g. EBGM) based on a background without statins by the score based on a background with statins. Mean masking ratios for all non-statins were calculated for each period allowing for direct comparison of score performance.

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Results: Masking ratios revealed that statin-rhabdomyolysis reporting in the background influenced signal detection results for non-statin-rhabdomyolysis pairs. For all time periods, the extent to which masking influenced mean point estimates was lower for EBGM than PRR and ROR. Mean masking ratios for PRR and ROR were nearly identical. The mean masking ratio peaked at 1.15 for EBGM and 1.44 for PRR and ROR in 2003. After 2003, mean masking ratios for all of the algorithms decreased over time (annualized decrease: EBGM 0.4% and PRR and ROR 1.7%) before trending towards a stable level.

Conclusions: Signal detection algorithms were not equally susceptible to masking based on masking ratios that directly compared the presence and absence of statins in the background. Mean masking ratios were lower for EBGM than PRR and ROR for all periods suggesting EBGM was influenced less by statin reporting. Mean masking ratios declined over time from their peak in 2003, and their stabilization suggests masking may persist.

782. Consumption Adjusted Reporting Rates of Adverse Drug Reactions in Norway

Kristian Svendsen.[1] *[1]Hospital Pharmacy of Tromsø, Tromsø, Norway.*

Background: While spontaneous reporting of adverse drug reaction (ADR) reports yield important information about the safety of drugs, information about the underlying use of the drug is often not available. Five reports in 1000 users do not equal five reports in 100 000 users.

Objectives: The aim of this project is to link consumption data from the Norwegian Prescription Registry (NorPD) with Norwegian data from the EudraVigilance (EV) database for ADR reports. The project will allow for comparison of reporting rates adjusted for the underlying use. Comparisons will be done between drugs, between different age groups and gender and between different ADRs.

Methods: The design of the project is a linked study of non-person-identifiable data from NorPD and EV. The only patient information that will be used is age and gender of drug user (NorPD) and patient in ADR reports. Data from 2004 to 2014 will be used from both data sources and the substances will be used for linkage. Various proportions and ratios will be calculated, the basic one will be reports/10000 users, and ratios between drugs and age groups/gender will be calculated for different research projects

Rules for filtering data will be created such as minimum number of reports and users to display data. A framework for conducting standardized analyses using the data will be created

Results: There are 1100 substances with one or more Norwegian ADR report in EV. These have been linked to ATC codes, and data from NorPD have been requested. Once data has been received, a single database will be created, and the first analyses using the data will be on elderly as a subgroup to see what ADRs get reported more in elderly when adjustment for consumption has been performed. This will be ready for ICPE in August.

Conclusions: While this project will not solve the unsolvable question of prevalence of ADR in the general population, it will yield a reporting rate per 10 000 users, and as such, it will give additional previously unknown data in Norway. The project can also generate hypotheses to be tested clinically such as the unknown reasons why specific ADRs are reported more often in specific sub-populations.

783. Sentinel Site Active Surveillance for First-Line Antiretroviral Medicines in Namibia

Marita Mann,[1] Assegid Mengistu,[2] Johannes Gaeseb,[3] Evans Sagwa,[4] Greatjoy Mazibuko,[4] Andy Stergachis.[5] *[1]Pharmacy, University of Washington, Seattle, WA, United States; [2]Therapeutics Information and Pharmacovigilance Centre, Ministry of Health & Social Services, Windhoek, Namibia; [3]Registrar of Medicines, Ministry of Health &Social Services, Windhoek, Namibia; [4]Management Sciences for Health, Windhoek, Namibia; [5]Global Medicines Program, University of Washington, Seattle, WA, United States.*

Background: Active surveillance pharmacovigilance estimates the incidence of adverse events and can generate useful information for effective decision-making within public health programs. Yet, there are few examples of active surveillance pharmacovigilance systems in low- and middle-income countries where the burden of many diseases and the need are greatest.

Objectives: The main objective of this study was to implement and evaluate an active surveillance

program for first-line antiretroviral therapy (ART) medicines in the sub-Saharan country of Namibia.

Methods: A prospective cohort study was designed and implemented at two sentinel ART treatment sites in Namibia. An active surveillance data collection form was developed and placed into the patient chart, adults naïve to ART were enrolled, and physicians recorded ART and health information during each follow-up visit, including actively recording the presence or absence of adverse events. Data quality was evaluated by comparing data collected to medical charts. The incidence of adverse events was assessed using Cox proportional hazard models.

Results: A total of 413 eligible patients were included from August 2012 to April 2013. The average age was 37 years; WHO clinical stage was I for 51% of patients, and mean baseline CD4 count was 216. The most common ART regimen was TDF/3TC/NVP. In total, 66 patients experienced 119 adverse events (AEs). The incidence of experiencing at least one AE was 0.3/100 person-years. Most common AEs were rash and abdominal pain. After adjustment for age, gender, WHO stage, and CD4 count, those WHO stage 2 had 8.8 times higher risk of experiencing an AE ($p = 0.01$, 95% CI 1.9–41.2) compared with those WHO stage 1. Age, gender, and CD4 count did not alter risk of experiencing an AE. On the active surveillance forms, demographic variables were missing less than 14% of patients, and follow-up visits were recorded for 82% of patients.

Conclusions: The incidence of adverse events to ART was low in this study population. With improved logistical considerations, such as incorporation of the active surveillance form into the medical record, a long-term, national active surveillance pharmacovigilance program could be successful.

784. Pharmacovigilance Data from Systematic Patient Reported Outcome (PRO) Tools Versus Usual Clinician Interactions: Are Cancer Patients Reporting Toxicity Data To Their Health Care Providers?

Joseph N Samuel[1], Tian Qi Wang[1], Andrea Perez-Cosio[2], M Catherine Brown[2], Ashlee Vennettilli[2], Nicholas Cheng[2], Gusharan Gill[2], Mindy Liang[2], Doris Howell[2], Wei Xu[2], Jack Seki[2], Geoffrey Liu[2].

[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada.

Background: Text mining and other tools are being introduced for use in electronic health records (EHR) to capture disease states in pharmacoepidemiology studies. To determine whether such approaches are appropriate for the collection of cancer-related toxicities (CRTs), two key questions require addressing: (i) Are healthcare providers and patients discussing these CRTs? (ii) Are these CRTs then reported in the EHR? We address the former question in this abstract.

Methods: 105 adult cancer outpatients (all cancer types) undergoing chemotherapy (Princess Margaret Cancer Centre) completed a systematic 59-item electronic patient-reported outcome tool to assess common CRTs (cross-sectional survey). Patients then engaged in their usual interactions with their healthcare providers, who were blinded from any of the patient-reported outcome tool data. Several days later, follow-up phone calls assessed whether there were discussions of any significant CRTs between patients and their providers.

Results: The median age was 54 years (range 19–85); 30% were male; 73% were Caucasian. The most prevalent moderate-severe chemotherapeutic toxicities were fatigue (85%), decreased appetite (62%), pain (52%), nausea (50%), and difficulty tasting food or drink (47%). Of all patients, 88% (95% CI: 81–94%) reported that their providers were aware and had discussed any moderate-severe CRTs with them. As a result of these discussions, 68% of patients had a change in management (addition of new drug, change in dosage, etc.). Of the remaining 32% patients, only 17% would have wanted a management change. In a subset of patients surveyed, 94% (95% CI: 86–102%) were satisfied/very satisfied that their providers had appropriately addressed any potential CRTs.

Conclusions: Through usual clinic encounters, the vast majority of providers addressed the major symptom-based CRTs of their cancer patients. This was further supported by high satisfaction rates. The next step will be a retrospective manual chart review to determine the completeness of reporting of such toxicities by providers in the EHR.

785. Studying Cancer as an Adverse Outcome from Nononcological Therapies: Review of the Food and Drug Administration's Postmarketing Commitment Database

Kirk D Midkiff,[1] David H Harris,[1] Alicia W Gilsenan,[1] Elizabeth B Andrews.[1] *[1]Pharmacoepidemiology and*

Therapeutic Risk Management, RTI Health Solutions, Research Triangle Park, NC, United States.

Background: Multiple stakeholders wish to know if medications increase the risk of cancer. Clinical trials and enhanced pharmacovigilance have limitations for studying cancer such as incomplete capture and high cost (for trials). Observational studies are used to characterize the risk of cancer but may be limited due to inadequate case identification, exposure assessment, and data sources, particularly for rare cancers. The ability to link patients to existing national cancer outcome data could be an ideal solution.

Objectives: Review postmarketing commitments (PMCs) to identify ones that may benefit from collaboration with cancer registries in the USA.

Methods: We reviewed the FDA PMC database to identify cancer outcomes under study in nononcological drugs. We reviewed drugs with an NDA/BLA approval date after 1994 and excluded drugs indicated for oncology treatments or supportive therapy or where an animal study or clinical trial was requested. We reviewed approval letters and other published material to characterize the therapeutic class, study design, and method for identifying cancer.

Results: Forty-six PMCs for 33 different drug entities were identified from the following drug classes: immunologic ($n=11$), endocrine and metabolic ($n=8$), dermatologic ($n=3$) and other ($n=11$). The most common cancer for the 12 entities that had a boxed warning for cancer was lymphoma ($n=7$), followed by thyroid C-cell tumor ($n=4$), other malignancies ($n=4$), skin cancer ($n=2$), and osteosarcoma ($n=1$). Study designs were not well described for all PMCs. Of the 46 PMCs, the most common method for identifying cancer was active surveillance of patients ($n=10$). Two studies mentioned cancer registries for long-term follow-up.

Conclusions: Postmarketing drug safety studies require the ability to properly identify and classify cancer outcomes over long periods. Linking treated cohorts from postapproval registries, database studies, or clinical trials to cancer registries at a national level could provide a scientifically robust way to efficiently and accurately quantify cancer risk.

786. Pharmacovigilance of Psychotropic Medicines in a Developing Country—A Prospective Surveillance

Ramesh Madhan,[1,2] Jisha Lucca,[1] Parthasarathi Gurumurthy.[1,2] *[1]Pharmacy Practice, JSS College of Pharmacy, Mysore, Karnataka, India; [2]Clinical Pharmacy, JSS Medical College Hospital, Mysore, Karnataka, India.*

Background: Psychotropic drugs are associated with significant short-term and long-term safety issues that may affect patients' mental health, physical health, and cost of care.

Objectives: This study was undertaken to identify and to monitor the adverse drug reactions (ADRs) to psychotropic medicines.

Methods: This was a prospective study conducted in ambulatory patients and in-patients of the psychiatry department of a tertiary care hospital. This study included patients of any age and either sex who presented with psychiatric illness as diagnosed by International Classification of Disease-10 and were receiving at least one psychotropic agent. The study involved both intensive and spontaneous reporting methods to identify ADRs. On identification of ADR (s), the case was discussed the concerned clinician, and all the required information was collected from patients' medical records and patient interview. Causality, severity, and preventability of reported ADR were assessed using standard scales.

Results: A total of 990 ADRs were identified in 613 patients from 1630 patients reviewed over a period of 24 months with an overall incidence rate of 37.6%. Of 990 ADRs, 69.4 % of the ADRs were detected by intensive monitoring while 30.5% of ADRs were received through spontaneous reporting. Antidepressants were the commonest group of agents implicated in ADRs (42%) followed by antipsychotics (41%). Escitalopram (15.9%) and olanzapine (12.1%) were the most commonly implicated medications. Most commonly involved system organ class was the gastrointestinal system (22.7%) followed by central and peripheral nervous system (17.8%). Dry mouth (10.2%), weight gain (8.18%), tremors (5.85%), and orthostatic hypotension (4.84%) were the commonly reported ADRs. Female gender ($p=0.002$), co-morbidities ($p=0.001$), and drug–drug interactions ($p=0.000$) were found as risk factors in developing ADRs in psychiatry patients. Upon causality assessment, 51.6% of the ADRs were "Probable," and 50% of them were "Mild" in severity. Of the ADRs, 76.7% were "Predictable" and 81.2% of them were "Not Preventable."

Conclusions: Patients receiving psychotropic medicines need routine monitoring to ensure their safety and adherence.

787. Impact of Adverse Drug Reactions on Daily Living of Patients on Anti-Psychotic Medications

Ramesh Madhan,[1,2] Jisha Lucca,[1] Parthasarathi Gurumurthy,[1,2] Himanshu Patel.[1,2] *[1]Pharmacy Practice, JSS College of Pharmacy, Mysore, Karnataka, India; [2]Clinical Pharmacy, JSS Medical College Hospital, Mysore, Karnataka, India.*

Background: Adverse drug reactions (ADRs) in psychiatry lead to poor quality of life and distract patients from maintaining medication adherence. It is essential to evaluate how ADRs to psychotropic medicines affect routine activities of patients.

Objectives: This study was conducted to assess the severity of ADRs to anti-psychotics and to study the impact of those ADRs on daily activities of patients.

Methods: This was a prospective study conducted for a period of twelve months at ambulatory care setting and in-patients wards of psychiatry department of a tertiary care hospital. A study included patients diagnosed with mental disorders according to International Classification of Diseases-10 criteria and on treatment with anti-psychotic medications for at least 6 weeks. Identified ADR(s) were discussed with a concerned clinician for authentication. The severity of ADRs was assessed using a standard scale. Impact of ADRs on daily living activities was assessed using Udvalg for Kliniske Undersogelser Side Effects Rating Scale and was categorized as "Mild," "Moderate," and "Markedly."

Results: A total of 405 ADRs were identified in 382 patients from 970 patients reviewed. Olanzapine (30%), quetiapine (22%), and amisulpride (22%) were drugs commonly associated with ADRs. Most commonly involved system organ classes were metabolic and nutritional disorders (25.5%) followed by central and peripheral nervous system (23%). Weight gain (21.8%), extra pyramidal symptoms (16.4%), menstrual irregularity (14.1%), and tremors (9.6%) were the common ADRs. Of the 353 ADRs assessed, majority (50%) of the ADRs were severe in nature followed by 32% moderate in severity. Sedation (10%), orthostatic hypotension (8%), galactorrhea (8%), tremors (7%), and extra pyramidal symptoms (5%) were found to be "markedly" affecting daily living of the patients. Weight gain (20%), hypersalivation (8%), and sexual dysfunctions (7%) were found to be "moderately" impacting on patients. Disturbances in daily activities due to ADRs were more in female patients.

Conclusions: ADRs to anti-psychotic medicines should be identified and managed on time to maintain healthy daily living in psychiatry patients.

788. Prospective Safety Monitoring of Drug-Drug Interactions: A Case Study of Warfarin and Selective Serotonin-Reuptake Inhibitors

Krista F Huybrechts,[1] Macarius M Donneyong,[1] Moa Park,[1] Joshua J Gagne,[1] Sebastian Schneeweiss,[1] Shirley Wang.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States.*

Background: Prospective surveillance systems, such as the FDA's Sentinel Program, are increasingly being used to monitor the safety of newly marketed medications. Such systems have not previously been used to assess outcomes of potential drug–drug interactions (DDIs).

Objectives: To explore the feasibility of using available prospective surveillance systems in a distributed data network to study DDIs, using the risk of bleeding associated with concurrent exposure to warfarin and selective serotonin-reuptake inhibitors (SSRIs) as a case study.

Methods: The distributed data network consisted of a US commercial (OptumClinformatics, 2004–2010) and public (PACE—Pharmaceutical Assistance Contract for the Elderly, 1994–2009) health insurance database, which were converted into the Mini-Sentinel Common Data Model. We customized the Prospective Routine Observational Monitoring Program Tools Propensity Score Matching tool, currently used by the FDA, to enable identification of patients exposed to both object and precipitant drugs. Specifically, among new users of warfarin (object drug), we identified patients who initiated an SSRI (precipitant drug) after a minimum of 60 days of continuous warfarin treatment. The 30-day risk of hospitalization for any major bleeding event was monitored on a quarterly basis in sequential cohorts of propensity score-matched warfarin initiators with and without concurrent SSRI exposure. Estimates were pooled across data sources.

Analyses of risk were restricted to the first 28 monitoring periods common to both data sources.

Results: The size of the matched cohorts increased from 131 patients in the first monitoring period to 22 754 in the last period. The relative risk of bleeding in the 1:100 variable ratio matched cohort started at 0.79 (95% confidence interval (CI), 0.04–15.70), increased to 3.86 (95% CI, 1.93–7.72) after 14 monitoring periods, and reached 1.80 (95% CI, 1.08–2.98) after 28 monitoring periods.

Conclusions: This case study of bleeding associated with concurrent exposure to warfarin and SSRIs—which was used as a positive control—illustrates that prospective surveillance systems can be customized to assess DDIs.

789. Rhabdomyolysis Could Be a Consequence of the Interaction Between Clonazepam and Other Antiepileptic Medications: A Pharmacovigilance Assessment

Ayad K Ali,[1] Mahyar Etminan.[2] [1]*Global Patient Safety, Eli Lilly and Company, Indianapolis, IN, United States;* [2]*Department of Pediatrics, Faculty of Medicine, Child and Family Research Institute, University of British Columbia, Vancouver, BC, Canada.*

Background: Epilepsy treatment involves frequent switching between antiepileptic medications (AM), and combination therapy with AM—including clonazepam—is common to control seizures. Therefore, the likelihood of adverse events, for example, rhabdomyolysis, due to interactions between AM is high. Striated muscle damage, including rhabdomyolysis, is a known risk for some AM, but it is unknown if the risk increases with concurrent clonazepam and other AM therapy.

Objectives: To assess the strength of interaction between clonazepam and other AM in terms of rhabdomyolysis adverse event reporting.

Methods: Adverse event reports that were submitted to the FDA Adverse Event Reporting System between 1997 and 2013 were used to apply multi-item gamma Poisson shrinker data mining algorithm to calculate the Interaction Signal Score (INTSS) between clonazepam and other AM in relation to rhabdomyolysis adverse event. AM were defined by the Anatomical Therapeutic Chemical classification code of "N03A," and rhabdomyolysis was defined by the Medical Dictionary for Regulatory Activities Preferred Term of "Rhabdomyolysis." Interaction threshold of INTSS >1.0 was selected to reflect the reporting of rhabdomyolysis due to the interaction between clonazepam and another AM being more than expected compared with the reporting when either medication was reported alone.

Results: A total of 10 interactions were identified for clonazepam with other AM corresponding to 190 reports. Among these, 15 reports mentioned clonazepam and phenobarbital concurrent exposure with an INTSS = 1.26 (64% females; mean age = 30, SD = 20), and 20 reports mentioned clonazepam and carbamazepine concomitant therapy with an INTSS = 1.15 (59% male; mean age = 42 years, SD = 18). Other combinations did not reach INTSS threshold. All clonazepam-related rhabdomyolysis events were serious, including fatal events for interaction with phenobarbital ($n = 2$) and with carbamazepine ($n = 7$).

Conclusions: Clonazepam should not be used with other AM with known rhabdomyolysis risk, particularly phenobarbital and carbamazepine. Pharmacoepidemiologic assessment is recommended to test the generated hypothesis of interaction.

790. Inverse Association Between Antiepileptic Drugs and Cancers; Data Mining of Large Medical Databases

Mitsutaka Takada,[1] Mai Fujimoto,[1] Migiwa Kanou,[1] Kouichi Hosomi.[1] [1]*School of Pharmacy, Kinki University, Higashi-osaka, Osaka, Japan.*

Background: Voltage-gated sodium channels are drug targets for the treatment of epilepsy. Recently, a decreased risk of cancer associated with voltage-gated sodium channel-inhibiting drug has been a focus of much interest.

Objectives: The purpose of the study is to test the hypothesis that the use of antiepileptic drugs may reduce the risk of cancers (bladder cancer, colorectal cancer, lung cancer, pancreatic cancer, gastric cancer, esophageal cancer, breast cancer, hematological malignancies, prostate cancer, and melanoma) by using different methodologies, algorithms, and databases.

Methods: A total of 54 841 322 drug–reaction pairs from the first quarter of 2004 through 2012 were

downloaded from the US Food and Drug Administration Adverse Event Reporting System, and a total of 4 019 652 drug–reaction pairs from 1965 through 2013 were downloaded from the Canada Vigilance Adverse Reaction Online Database. For these two spontaneous reporting databases, the reporting odds ratio and the information component were used to detect an inverse association between antiepileptic drugs and cancers. The upper limit of the 95% confidence interval of reporting odds ratio <1 and information component <0 signified an inverse association. Furthermore, by using the claims database, which contains 1.2 million insured persons, the event sequence symmetry analysis was performed to identify an inverse association between antiepileptic drugs and cancers over the period of January 2005 to July 2013. The upper limit of the 95% confidence interval of adjusted sequence ratio <1 signified an inverse association.

Results: Significant inverse associations were found between antiepileptic drugs and cancers including colorectal cancer, lung cancer, pancreatic cancer, hematological malignancies, breast cancer, and prostate cancer. Positive association between antiepileptic drugs and cancer was not found.

Conclusions: Multi-methodological approaches using different methodologies, algorithms, and databases suggested that antiepileptic drugs were associated with the decreased risks for cancers. Further studies are needed to confirm our findings and elucidate the mechanism for anti-cancer effect of antiepileptic drugs.

791. Patterns in Spontaneous Adverse Event Reporting Among Branded and Generic Antiepileptic Drugs

Justin Bohn,[1,2,3] Cindy Kortepeter,[3] Monica Muñoz,[3] Kelley Simms,[3] Susan Montenegro,[3] Gerald Dal Pan.[3] *[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States; [3]Office of Surveillance and Epidemiology, Food and Drug Administration, Silver Spring, MD, United States.*

Background: Spontaneous adverse event reports constitute an important source of information on previously unknown adverse reactions to marketed medicines. However, the dynamics of such reporting following generic introduction are poorly understood. Furthermore, it remains unclear if data quality in current spontaneous reporting systems is adequate to enable generic pharmacovigilance.

Objectives: Using adverse event (AE) reports on five antiepileptic drugs (AEDs) from FDA's Adverse Event Reporting System (FAERS), we (1) characterize the evolution of spontaneous AE reporting patterns as generic AEDs become available and (2) determine the extent and quality of product-identifying information in such reports.

Methods: We identified 34 746 reports in FAERS listing any of five AEDs (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, and topiramate) as a suspect product in a domestic serious AE. We examined trends in the sender composition of reports received before and after generic approval and compared against trends in utilization. In order to assess product-identifying information contained in the FAERS reports, we manually reviewed 2500 randomly-selected reports of serious adverse events in the USA and scored them on five dimensions according to the extent of information contained in their narrative fields.

Results: Before generic approval, 69.9% of reports were submitted by innovator manufacturers. After generic approval, 55.4% of reports were submitted by innovators while only 9.9% of reports were submitted by generic manufacturers, despite majority generic dispensing. After generic approval, the proportion of reports originating with consumer reports was much higher among innovator-submitted reports (42.5%) than among generic-submitted reports (12.3%). Among 2500 manually reviewed reports, the suspect product type (brand or generic) could not be determined in 84% of reports, while generic products (16%) were identified more often than brand-name products (less than 1%).

Conclusions: Spontaneous AE reports rarely contain adequate product-identifying information to support generic pharmacovigilance. Stakeholders should act to promote more detailed reporting practices.

792. Psychotropic Drug–Drug Interactions in Three Most Commonly Used Drug Information Databases

Xinyue Liu,[1] Marie Barnicoat,[1] Regina Bussing,[2] Almut G Winterstein.[1,3] *[1]Pharmaceutical Outcomes*

& Policy, College of Pharmacy, University of Florida, Gainesville, FL, United States; [2]Psychiatry, College of Medicine, University of Florida, Gainesville, FL, United States; [3]Epidemiology, Colleges of Medicine and Public Health & Health Professions, Gainesville, FL, United States.

Background: Information on psychotropic drug–drug interactions in drug information databases provides valuable information to clinicians, but the consistency of these warnings in different databases is unknown.

Objectives: To evaluate the consistency of psychotropic drug–drug interactions in three commonly used drug information databases: Clinical Pharmacology, Micromedex, and Lexicomp.

Methods: We extracted drug–drug interactions for 150 psychotropic drugs from the aforementioned three databases. Psychotropic drug classes included central nervous system stimulants, antidepressants, antipsychotics, anticonvulsants, and anxiolytics/sedatives/hypnotics. To increase clinical significance, we restricted analyses to "major/severe" interactions, requiring the level of severity be severe or major in Clinical Pharmacology, contraindicated or major in Micromedex, and X and D in Lexicomp. We matched the "major/severe" psychotropic drug–drug interactions across the three databases and summarized the major content of these interactions.

Results: We identified 1432, 241, and 666 psychotropic drug–drug or drug–class interactions from Clinical Pharmacology, Micromedex, and Lexicomp, respectively. Only 106 drug–drug or drug–class interactions were present across all three databases. Common adverse outcomes caused by psychotropic drug–drug interactions included increased/decreased effectiveness, central nervous system depression, neurotoxicity, QT prolongation, serotonin syndrome, and multiple adverse reactions. During the time span we conducted our analysis, several interactions were updated, including upgrading/downgrading/removal of the interactions.

Conclusions: The consistency of psychotropic drug–drug interaction documentation across Clinical Pharmacology, Micromedex, and Lexicomp is unsatisfactory. More evidence for severity assignment and the clinical significance of interactions is needed to facilitate clinical use of the information.

793. Polypharmacy in Spontaneous Reports of Over-the-Counter (OTC) Products: Skin Care

Mary E Ritchey,[1] Leslie Rylander,[1] Michael Steinbuch.[1] *[1]Global Safety Surveillance and Analysis, Procter & Gamble, Cincinnati, OH, United States.*

Background: Over-the-counters are low-risk products used by generally healthy people; thus, they may provide an opportunity to assess the effects of polypharmacy in the absence of underlying conditions and competing risks.

Objectives: We wanted to understand whether using more products is associated with increased adverse event (AE) reporting in our spontaneous reporting system (SRS). We chose skin care products (SKP) for assessment because consumers tend to use multiple SKP without attributing reported outcomes to a single product.

Methods: We limited our SRS to only relevant case data for the 10 most frequently reported SKP. We tallied how often these SKP were used alone or in combination as well as MedDRA preferred terms (PTs) associated with AE cases. Further, we compared the top five PT for specific SKP and combinations using the reporting odds ratios (ROR) and 95% confidence intervals (CI).

Results: The dataset for 10 top SKP contained 4563 AE cases with 37 950 PTs. Of these, one SKP was seen in 2159 cases, two SKP in 1496 cases, three SKP in 833 cases, and four SKP in 75 cases. The mean number of PT was 4.5–5, irrespective of the number of SKP used.

The top five PTs were erythema, pruritus, hypersensitivity, rash, and acne. An association was noted between the number of SKP and erythema, hypersensitivity, and rash (Mantel–Haenszel and Pearson $\chi^2 < 0.05$). The ROR analysis revealed a general increase with the addition of a second SKP; however, this was not always observed. No clear increase was noted with the addition of a third or fourth SKP. In fact, a potential antagonistic interaction was seen for erythema with one group of three SKP (ROR decreased from 2.05 (CI 1.15, 3.61) with one SKP to 1.39 (CI 1.04–1.85) with three SKP). Increased ROR with two or three SKP occurred more frequently for erythema, pruritus, and hypersensitivity.

Conclusions: Reporting of AE in SRS for SKP suggests increased RORs may not be related to concomitant use of these products. Further work is warranted to understand potential interactions between SKP, including expanding to our full SRS, data mining including SKP across multiple manufacturers, and evaluation beyond spontaneous reports.

794. Comparison of Inhibitors of Dipeptidylpeptidase 4 (DDP-4 Inhibitors or Gliptins) Marketed By Indian Companies With the Original SmPC from Innovator Companies

Nilima P Justice, Pipasha N Biswas.

Pharmacovigilance & Risk Management, Mannkind Corporation, Paramus, NJ, United States; Pharmacovigilance & Pharmacoepidemiology, Symogen Limited, Bourne End, Buckinghamshire, United Kingdom.

Background: There are currently four agents that inhibit dipeptidylpeptidase 4 (DDP-4) available to patients with diabetes. Linagliptin (Trajenta) is still included in the Medicines and Healthcare products Regulatory Agency black triangle scheme and so is being intensively monitored. Sitagliptin (Januvia), saxagliptin (Onglyza), and vildagliptin (Galvus) products were removed from the black triangle list during the second half of 2012. In an era where consumer awareness is at an all-time high and rapidly increasing, information available to patients and prescribers for safe and efficient use of medicines is still an area of concern.

Objectives: Compare the PILs of DDP-4 inhibitors from Indian generic companies with that of SmPCs of innovator companies and review if the package inserts adhere to standard guidelines.

Methods: To collect unbiased information, PILs for DDP-4 inhibitor drugs were downloaded from the Internet and compared directly with SmPCs of the innovator companies for each section and missing information highlighted. Sitagliptin and Vildagliptin are the drugs for which the SmPC and PI were compared as these are the only generics available in India.

Results: Documents compared showed standard labeling guidelines were not adhered and details not updated on the PILs for generic drugs. Discrepancies were found in undesirable effects section, contraindication, special warnings, precautions for use, and interaction with other drugs. Serious adverse events, that is, serious hypersensitive reactions, hepatic abnormalities, serious skin reactions including SJS/exfoliative skin lesions, and fatal and non-fatal haemorrhagic and necrotizing pancreatitis were missing in the PIL for drugs manufactured by the Indian generic companies when compared with the innovator companies.

Conclusions: Our research has highlighted that Indian generic companies do not have any mechanism or process for development of package inserts with important sections on safety of these drugs missing with several discrepancies. Provision of good quality patient information is intended to supplement and not replace the advice given to patients by health professionals.

795. Allergic Reactions Associated With Herbal Remedies in the WHO-UMC Pharmacovigilance Database

Jitka Pokladnikova,[1] Ricarda Meincke,[1,2] Ronald Meyboom,[3,4] Stefan Russmann.[2,5] *[1]Social and Clinical Pharmacy, Charles University Prague, Hradec Kralove, Czech Republic; [2]Clinical Pharmacology and Toxicology, University Hospital Zurich, Zurich, Switzerland; [3]Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, Netherlands; [4]Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden; [5]Pharmaceutical Sciences, Swiss Federal Institute of Technology (ETHZ), Zurich, Switzerland.*

Background: Herbal remedies are used worldwide for the treatment of a large range of medical disorders, but they are poorly represented in population-based pharmacoepidemiological databases. Although often perceived as well-tolerated treatments, they can also cause serious and even life-threatening allergic reactions.

Objectives: We aimed to investigate reporting patterns of immediate-type allergic reactions associated with herbal remedies in a database of spontaneous reports.

Methods: We analyzed all adverse drug reactions (ADRs) involving herbals reported from 1969 to August 2014 to the WHO-UMC pharmacovigilance database. Our analyses included only ADRs where herbals that we had validated were the reported suspect cause and with possible, probable, or certain causality assessment. Furthermore, we included only ADRs with WHOART reaction terms that indicated high specificity regarding immediate-type allergic reactions and with a reported latency time of no more than 1 day.

Results: Within the initial dataset containing 26 909 unique reports with 237 496 ADR, we identified 892 reports (66.3% on females) with 1253 ADRs that met our inclusion criteria. Only four countries contributed the majority (57.3%) of all reports (Germany 21.8%, Australia 12.8%, Sweden 11.6%, and Thailand 11.2%). Most frequently reported immediate-type

allergic reactions were urticaria and rash (44.5%). Anaphylactic reactions accounted for 16.3%, including 60 reports of anaphylactic shock, and asthmatic reactions for 5.8%. Most frequently involved herbals were mixed preparations (46.9%) including herbal pollen and *Phleum pratense* (timothy-grass, 5.4%) that are frequently used for desensitization therapy, and *Andrographis paniculata* (4.2%) typically used for treatment of the common cold. Additional ADR with gastrointestinal symptoms were also found, which were compatible but unspecific for an allergic reaction in the studied database.

Conclusions: The WHO-UMC pharmacovigilance database is one of the largest collections of allergic reactions to herbals and a valuable resource for their qualitative descriptive study. Health care professionals and patients should be aware of ADR associated with herbals and be encouraged to report them.

796. Withdrawn by Author

797. Development of a Research Network and an Infrastructure for the Nationwide Registry Study in Palliative Care in Japan

Keisuke Ariyoshi,[1,5] Tempei Miyaji,[2,5] Isseki Maeda,[3] Satoru Iwase,[1] Takuhiro Yamaguchi.[2,4,5] *[1]Department of Palliative Medicine, Research Hospital of the Institute of Medical Science, The University of Tokyo, Tokyo, Japan; [2]Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [3]Department of Palliative Medicine, Osaka University Graduate School of Medicine, Osaka, Japan; [4]Biostatistics, Tohoku University Graduate School of Medicine, Miyagi, Japan; [5]Data Center, Japanese Organisation for Research and Treatment of Cancer (JORTC), Tokyo.*

Background: Palliative care (PC) in Japan is a specialty field poor in research resources and expertise. Meanwhile, conducting interventional trials is difficult in this field; registry studies would provide benefit and toxicity data on widespread and longer-term medication and be helpful to identify population in which a drug effect/occurrence of adverse event is more likely.

Development of a research network and an infrastructure is needed; however, there were few support organizations specialized for PC research.

Objectives: To develop a research network and an infrastructure for a multicenter registry study that can prospectively and consecutively evaluate the effectiveness and safety of palliative medicine in real-world practice.

Methods: A steering committee (SC), which consists of a principal investigator, a biostatistician, and a clinical data manager, was launched in October 2014. Selected nationwide were 41 participating facilities including hospice, inpatient palliative care unit, hospital palliative care team, and psycho-oncology group, and kick-off meetings were held in January and February 2015. We planned to use an electronic data capturing system for information management. A nonprofit organization, the Japanese Organisation for Research and Treatment of Cancer, which was founded to support PC researches, provided support for developing the infrastructure.

Results: By the initiative of the SC, recruitment of participating facilities, selection of outcomes and measurement scales, and statistical analysis planning were coming along smoothly. Understanding of study objectives and logistics was promoted and recognized through the kick-off meetings.

The SC selected with support of the Japanese Organisation for Research and Treatment of Cancer a valid and user-friendly electronic data capturing system, which is consistent with the study purpose.

Conclusions: We successfully developed a research network and an infrastructure for the nationwide registry study.

Organized support by experts in biostatistics and clinical data management would be of great value to establish research framework in PC in Japan.

Acknowledgments

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798. Using the Earliest Available Claims Data for Influenza Vaccine Safety Surveillance in Mini-Sentinel

W Katherine Yih,[1] Lauren Zichittella,[1] Sukhminder K Sandhu,[2] Michael Nguyen,[2] Martin Kulldorff,[1] David V Cole,[1] Robert Jin,[1] Alison T Kawai,[1] Cheryl N McMahill-Walraven,[3] Nandini Selvam,[4] Mano S Selvan[5], Grace M Lee.[1,6] *[1]Harvard Pilgrim Health Care Institute and Department of Population Medicine, Harvard Medical School, Boston, MA, United States; [2]Center for Biologics Evaluation and Research, Food and Drug Administration, Silver*

Spring, MD, United States; [3]Data Science, Aetna, Blue Bell, PA, United States; [4]Government and Academic Research, HealthCore, Alexandria, VA, United States; [5]Comprehensive Health Insights, Humana, Louisville, KY, United States; [6]Division of Infectious Diseases and Department of Laboratory Medicine, Children's Hospital Boston, Boston, MA, United States.

Background: The Mini-Sentinel program partners with large health insurers to monitor drug and vaccine safety in collaboration with the FDA. Data are mature (received >6 months after care-date) and updated quarterly. In public health emergencies, access to more timely healthcare data is critical to support regulatory decision-making.

Objectives: To develop the infrastructure to conduct timely sequential surveillance for safety of influenza vaccines and other medical countermeasures.

Methods: Three data partners provided their earliest available ("fresh") claims data on cumulative influenza vaccination and health outcomes on a staggered bi-monthly basis during the 2013–14 influenza season. Vaccination data from eight state immunization registries were also incorporated. We monitored rates of anaphylaxis in the entire population using the cohort design and rates of seizures in children ≤4 years of age using both the self-controlled risk interval design (primary) and, to enhance timeliness of potential signals, the cohort design (secondary). After each of 10 data updates, we conducted sequential analysis for inactivated (IIV) and live (LAIV) influenza vaccines using the maxSPRT method. Adjustments were made for data-lag to minimize bias.

Results: Most of the 10 sequential analyses were conducted within 6 weeks of the last care-date in the cumulative dataset. Captured were 6 682 336 doses of IIV and 782 125 of LAIV. The primary analyses did not identify any statistical signal for anaphylaxis or seizures following IIV or LAIV. Similar to prior studies, the risk of seizures was higher following concomitant IIV and PCV13 in 6- to 23-month-olds (cohort analysis) compared with historical IIV vaccinees without concomitant PCV13 (RR = 2.7). Limitations of employing fresh data for surveillance include cost and the need for careful scrutiny of signals.

Conclusions: Mini-Sentinel can implement a sequential analysis system that uses fresh data for medical product safety surveillance. The relative strengths and limitations of using fresh versus settled data should be considered in deciding when to use such a system.

799. Long-Acting Bronchodilators and Risk of Adverse Cardiovascular Events in Chronic Obstructive Pulmonary Disease: A Focused Critical Review

Sunning Tao,[1] Erika Kirsch,[1] Karen Yeomans,[1] Catherine Sigler.[2] *[1]Value Demonstration, UBC: An Express Scripts Company, Montreal, Quebec, Canada; [2]Safety, Epidemiology, Registries and Risk Management, UBC: An Express Scripts Company, Blue Bell, Pennsylvania, United States.*

Background: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. Long-acting bronchodilators (LABs) are the mainstay of pharmacological maintenance therapy for COPD. However, the possibility that use of LABs may lead to risk of cardiovascular events remains debated.

Objectives: The objective is to provide a critical review of methodologies employed to evaluate risk of cardiovascular events in patients with COPD using LABs.

Methods: A targeted search was conducted in PubMed to identify all original published research reporting adverse cardiovascular events from clinical trials and observational studies. The search was limited to English language, but not restricted by publication date. Selected abstracts were reviewed for study population, treatment, follow-up duration, study design, and cardiovascular events.

Results: The search returned 131 citations, of which 19 reported results from original research. Among them, 10 studies (53%) were clinical trials and 9 (47%) were observational studies. For the clinical trials, sample sizes ranged from 204 to 6184 patients; follow-up duration was 14 days to 4 years. For the observational studies, six (67%) were nested case-control studies, two (22%) cohort studies, and one (11%) self-controlled case series study; sample sizes ranged from 1043 to 352 631 patients; follow-up duration was 52 weeks to 13 years. The most frequently reported cardiovascular events included arrhythmias, stroke, angina, myocardial infarction, and cardiovascular death. While none of the clinical trials showed a

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statistically significant association between the use of LABs and increased risk of cardiovascular events, five observational studies did.

Conclusions: The controversy continues regarding the use of LABs and their cardiovascular safety. Short follow-up duration and exclusion of patients with previous history of cardiovascular events are the main limitations to clinical trials, while observational studies may be limited by residual confounding by disease severity and immeasurable time bias. A well-designed observational study is warranted.

800. Comparison of Benefit-Risk Assessment Methods for Prospective Monitoring of Newly Marketed Drugs: A Simulation Study

Joshua J. Gagne,[1] Mehdi Najafzadeh,[1] Niteesh K. Choudhry,[1] Katsiaryna Bykov,[1] Kristijan H. Kahler,[2] Diane Martin,[2] James R. Rogers,[1] Sebastian Schneeweiss.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.*

Background: Information required for market approval is not necessarily sufficient for subsequent coverage and treatment decisions. Simultaneously incorporating benefits and risks in a prospective monitoring framework can aid decision makers in determining whether and when sufficient evidence exits to indicate that one drug is favorable over another.

Objectives: To compare benefit-risk assessment (BRA) methods for determining whether and when sufficient evidence exists to indicate that one drug is net favorable over another in prospective monitoring.

Methods: We simulated prospective monitoring of a new drug (A) versus an alternative (B) with respect to two beneficial and three harmful outcomes. We generated data for 1000 iterations of six scenarios – each with different relative benefit-risk profiles of drug A versus B – and applied four BRA metrics: number needed to treat and number needed to harm (NNT|NNH); incremental net benefit (INB) with maximum acceptable risk (INB-MAR); INB with relative-value adjusted life years (INB-RVALY); and INB with quality-adjusted life years (INB-QALY). We determined the proportion of iterations in which the 99% confidence interval (CI) for each metric included and excluded the null (indicating net favorability of one drug), and we calculated mean time-to-alerting.

Results: With no true difference in any outcome between drugs A and B, the proportion of iterations including the null was lowest for INB-RVALY (64%) and highest for INB-QALY (76%). When drug A was more effective and the drugs were equally safe, INB-QALY indicated net favorability of drug A in 81% of iterations, INB-MAR and INB-RVALY indicated net favorability in 79% of iterations, and NNT|NNH indicated net favorability in 72% of iterations. When drug A was safer than drug B, NNT|NNH had the highest proportion of iterations indicating net favorability of drug A (65%). Mean time-to-alerting was similar among methods across the six scenarios.

Conclusions: BRA metrics can be useful for identifying net favorability when applied to prospective monitoring of a new drug versus an alternative. INB-based approaches similarly outperform unweighted NNT|NNH approaches.

801. Benefit-Risk Analysis and Management Plan for Rare Serious Adverse Events (SAEs): Progressive Multifocal Leukoencephalopathy (PML) Case Example

Deanna Hill,[1] Amanda Eudy,[1,2] Dimitri Bennett,[1] Jonathon Haddad,[3] Barbara Haight,[4] Sarah Kavanagh,[3] Christi Kleoudis,[3] Eric Lewis,[4] Susan Duke.[4] *[1]Worldwide Epidemiology, GlaxoSmithKline (GSK), Collegeville, PA, USA; [2]Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]Quantitative Sciences, GlaxoSmithKline, Research Triangle Park, NC, USA; [4]Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline, Research Triangle Park, NC, USA.*

Background: Rare, potentially drug-related SAEs are of particular concern for regulatory authorities and sponsors. It is often challenging to assess the benefit-risk profile of treatments where these SAEs occur.

Objectives: To describe methods undertaken to contextualize the risk of a rare SAE, using PML as an example, and evaluate an asset's benefit-risk profile.

Methods: An internal GSK cross-functional working group composed of pharmacovigilance scientists/physicians, statisticians and epidemiologists

developed a benefit-risk management and analysis plan guidance document to assess whether treatments of interest increase the risk of PML above what would be expected in the treated population.

Results: Steps to evaluate the benefit-risk profile:

(1) Describe the pathogenesis of the rare SAE (PML as the case example);
(2) Establish diagnostic criteria;
(3) Conduct a systematic literature review to assess the risk associated with medical conditions of interest and the medications used to treat those conditions;
(4) Employ an appropriate statistical method to predict expected rates of rare events in a population and whether the rate seen with a treatment of interest is expected or in excess. Statistical methods have included binomial probabilities and risk ratios;
(5) Apply methods to evaluate benefit-risk profile including:
    a. Value Tree to identify key benefits and risks in relation to other treatment options;
    b. Graphical displays (e.g., Forest Plots, Norton Heat Map/quantitative methods [i.e., Multi-Criteria Decision Analysis (MCDA)]);

Graphical presentations can help stakeholders synthesize results from multiple sources/endpoint(s). MCDA assesses multiple risks and benefits simultaneously by identifying critical favorable and unfavorable outcomes, assigning relative weights based on their importance, and providing a quantitative assessment of the benefit-risk profile

(6) Establish a risk mitigation plan, including appropriate screening, monitoring and education.

Conclusions: A systematic approach to benefit-risk analysis and management helps characterize rare SAEs and put them into context relative to benefits and background risks.

802. Direct-To-Consumer Advertising of Medicines in Singapore: Understanding Awareness, Perception and Behavior among the General Public

Cheong Hian Goh,[1] Mui-Ling Tan,[2] Terence Tze-Yin Fong,[2] Wai-Ping Yau.[2] *[1]Health Sciences Authority, Singapore, Singapore; [2]Department of Pharmacy, National University of Singapore, Singapore, Singapore.*

Background: Direct-to-consumer advertising (DTCA) of medicines refers to the marketing of medicines that are directed at patients, and delivered through different media. While common in the USA, there is limited information about these aspects on the general public locally.

Objectives: To gather information on the general public's awareness, perception and behaviour towards direct-to consumer advertising of medicines in Singapore.

Methods: A cross-sectional survey was conducted using self-administered questionnaire at various public locations in Singapore to achieve a sample size of 384. The pilot-tested questionnaire was developed by adapting sections of validated questionnaires from other studies and revised where necessary. Descriptive statistics were generated to summarize the data.

Results: Of the general public surveyed in December 2014, majority were Singaporean (83.1%), Chinese (74.1%) by race/ethnic group, had used some form of healthcare payment method (87.8%), with the distribution of the age groups similar to the national statistics. Of the 194 respondents who were aware of DTCA, most came across from broadcast media, TV in particular (83.5%), to a lesser extent from printed materials (magazines, newspapers) (36.6%) and outdoors media (e.g., billboard, posters, and advertising on buses) (36.2%), and the least observed on the Internet (8.0%). It was found that those who have seen an advertisement for medications would generally seek medical clarification with healthcare practitioners and pharmacists. Additionally, a large proportion ($n = 268$ or 84.0%) perceived that information of all ads for medications must be approved by the licencing authority before those ads are used.

Conclusions: While the general public in Singapore may be relatively unfamiliar with DTCA, the finding suggests the potential outreach and influences of broadcast media, particularly TV in disseminating healthcare information. The results also underscore the public's confidence and reliance on the regulatory agency to control medical advertising, and the role of healthcare professionals to advise the public on the informed choices of the DTCA.

803. Patient Knowledge of Safe Use of ER/LA Opioid Analgesics Following Implementation of the Class-Wide REMS

Daina B. Esposito,[1] Judith J. Stephenson,[1] M Soledad Cepeda,[2] Paul M. Coplan,[3] Jennifer C.L. Hawes,[1] Crystal N. Holick,[1] Jean-Yves Maziere,[4] Gregory P. Wedin,[5] Stephan F. Lanes.[1] *[1]HealthCore, Inc., Andover, MA, USA; [2]Janssen Research and Development, Titusville, NJ, USA; [3]Purdue Pharma, LP, Stamford, CT, USA; [4]Roxane Laboratories, Columbus, OH, USA; [5]Upsher-Smith Laboratories, Inc., Maple Grove, MN, USA.*

Background: Extended release (ER) and long-acting (LA) opioid analgesics are approved in the USA for the management of chronic moderate-to-severe pain. A Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics was implemented in 2012.

Objectives: To assess whether patients received and understood the Medication Guide and/or Patient Counseling Document (PCD), patient knowledge of the safe use of ER/LA opioid analgesics, and factors that influence knowledge and satisfaction with access to treatment.

Methods: We identified from administrative claims in the HealthCore Integrated Research Database™ patients who filled at least one prescription for an ER/LA opioid analgesic between 01 December 2012 and 30 November 2013. Patients completed a survey about their use of and knowledge of ER/LA opioid analgesics. We described respondents, calculated a Knowledge Assessment Score (KAS), and assessed factors associated with poor knowledge of safe ER/LA opioid analgesic use.

Results: There were 413 patients surveyed. Among 405 respondents, 92% received and 97% read a Medication Guide, while 45% received or had a provider reference the PCD. Only 56% were counseled about safe discontinuation and 48% were counseled about disposal of unused opioids. Mean KAS was 85.6% (standard deviation [SD] 10.38%). Patients prescribed opioids not by a pain specialist were more likely to have a lower KAS (odds ratio [OR] 2.70, 95% confidence interval [CI] 1.13–6.44). Although 82% of patients reported satisfaction with access to treatment, nearly half felt that they needed to see a provider too often to obtain medication.

Conclusions: The ER/LA opioid REMS was effective in getting the Medication Guide to patients, and patients were knowledgeable about safe use of ER/LA opioid analgesics. The PCD was less widely used, and reported counseling about discontinuation and disposal was limited. Patients reported general satisfaction with access to ER/LA opioids. The REMS tools appear to be effective in conveying key safety messages to patients.

804. Impact of Risk Minimisation Measures on Citalopram Use in Two European Countries

Inge Zomerdijk, Gianluca Trifirò, Sabine Straus, Miriam Sturkenboom.

Erasmus University Medical Center, Rotterdam, Netherlands; Medicines Evaluation Board, Utrecht, The Netherlands.

Background: In October 2011, dose restrictions were recommended to minimise the dose-dependent risk of QT interval prolongation associated with citalopram. The maximum daily dose was reduced from 60 to 40 mg and in patients aged ≥65 years from 40 to 20 mg. This was communicated to prescribers in a direct healthcare professional communication (DHPC).

Objectives: To assess the impact of these recommendations on the use of citalopram in the Netherlands (NL) and the United Kingdom (UK).

Methods: A retrospective population-based study was conducted within primary care databases in NL (IPCI: 1998–2012) and UK (THIN: 1996–2013). Monthly prevalence and incidence rates of citalopram use were calculated (users/1000 person years (PY)) and stratified by country, age group (<65; ≥65) and daily dose category ≤20 mg (low); >20 to ≤40 mg (moderate); >40 mg (high). Interrupted time-series analysis using an ARIMA model was performed to assess the effect of the dose restrictions on the use of citalopram.

Results: The overall prevalence rate of citalopram use was higher in UK compared with NL (11.1 vs. 3.7 users per 1000 PY). These rates were highest for low dose citalopram,10.8 vs. 3.3 users per 1000 PY, and lowest for high dose citalopram, 0.3 vs. 0.1 users per 1000 PY, in UK and NL, respectively . After the recommended dose restriction, in the population ≥65 years citalopram use with moderate dosage significantly decreased both in UK and NL. In UK, this was also observed for the high dose in this older population. Both in UK and NL, among population <65 years, the use of high dose significantly reduced, while low and moderate dosages did not decrease significantly. The monthly rates of new citalopram users

reduced after the dose restrictions in both countries and irrespective of age categories. A significant reduction was however only observed in the British population aged ≥65 years.

Conclusions: Following the recommended dose restrictions communicated by DHPC in October 2011, the use of high and moderate dose citalopram decreased in UK as well as NL. The effects seemed to be stronger in UK compared to NL, which may be due to the higher prevalent use of citalopram in the UK compared to NL.

805. Diabetes Testing for Adults Taking Antipsychotic Drugs: Where to Target Risk Minimization Interventions

Elaine H. Morrato,[1] Elizabeth Campagna,[2] Sarah Brewer,[2] Miriam Dickinson,[2] Deborah Thomas,[3] Richard C. Lindrooth.[1] *[1]Health Systems, Management and Policy, Colorado School of Public Health, Aurora, CO, USA; [2]Adult and Child Center for Health Outcomes Research and Delivery Science, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [3]University of Colorado Denver, Auraria Campus, Denver, CO, USA.*

Background: Adults taking antipsychotics are at increased risk for developing diabetes. Reported glucose testing rates are low. It is not known which patient, provider or practice factors are the key determinants of low rates of testing.

Objectives: To assess the relative association of hypothesized factors affecting testing and inform risk minimization efforts.

Methods: A retrospective cohort study was conducted among new users (ages 18–64 years) of second-generation antipsychotics in Missouri Medicaid ($N = 1813$ patients) using administrative claims data (2010–2012) linked with physician/practice market data and a prescriber knowledge, attitudes, and behavior survey. Annual glucose testing was defined as a claim for an A1c or glucose lab test occurring within ±180 days of the index antipsychotic claim. Multivariable logistic regression was performed to identify factors associated ($p < 0.05$) with no testing.

Results: The annual glucose testing rate was 79%. The odds of no testing were higher in males (AOR = 1.38); lower in adults >40 years (AOR range = 0.54–0.66); lower in adults with more co-morbidity (>4 mental health diagnostic categories vs. 0–1 (AOR = 0.32), diabetes (AOR = 0.31), dyslipidemia (AOR = 0.25), hypertension (AOR = 0.47)); and lower in frequent users of the healthcare system (>6 outpatient encounters vs. none (AOR = 0.34), 6–12 inpatient/emergency department encounters versus <6 (AOR = 0.52)). Lower odds of no testing were seen if the index prescriber was a primary care provider versus private mental health provider (AOR = 0.45) and if the patient received care during the study period at a Community Mental Health Center (AOR = 0.58). Use of electronic health records, shared mental/medical health facilities, and prescriber attitudes and behavioral intent were not associated with testing after adjusting for patient factors.

Conclusions: Higher rates of glucose testing were found compared to prior reports indicating progress in mitigating diabetes risks among patients taking antipsychotics. Interventions to fully achieve population-based screening goals should target younger, healthier adults receiving antipsychotics to support primary prevention in these at-risk patients.

806. Primary Care Physicians and Prescription Opioid Abuse: A National Survey

Catherine S. Hwang,[1,2] Lydia W. Turner,[1,2] Stefan P. Kruszewski,[1,3,4] Andrew Kolodny,[5] G Caleb Alexander.[1,2,6] *[1]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [3]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4]Phoenix House Foundation, New York, NY, USA; [5]Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, USA.*

Background: Physicians are a key stakeholder in the epidemic of prescription opioid abuse.

Objectives: We assessed physicians' knowledge of opioid abuse and diversion, as well as their support for clinical and regulatory interventions to reduce opioid-related injuries and deaths.

Methods: We used the Dillman method to conduct a nationally representative mail survey of 1000 practicing primary care physicians in the USA. Participants were sent a 45-item questionnaire, $2 cash incentive,

and reply envelope in February 2014. Two subsequent waves of the survey were mailed to non-respondents approximately 6 and 12 weeks after the first wave. We did not find evidence of non-response bias, but assigned post-stratification weights in our analyses to account for modest differences in response rates based on specialty and country of training.

Results: The adjusted response rate was 58%. All physicians (100%) believed that prescription drug abuse was a problem in their communities, with more than one-half (53%) reporting that it was "a big problem". However, one-third (34%) incorrectly reported that the most common route of abuse was other than swallowing pills whole, nearly one-half (46%) erroneously reported that abuse-deterrent formulations were less addictive than their counterparts, and one-fourth (25%) reported being not at all or only slightly concerned about the potential for opioid diversion from the licit to the illicit market. Most physicians supported clinical and regulatory interventions to reduce prescription opioid abuse, including the use of patient contracts (98%), urine drug testing (90%), requiring prescribers to check a centralized database prior to prescribing opioids (88%), and instituting greater restrictions on the marketing and promotion of opioids (77–82%). Despite this, one-third of physicians (33%) believed that interventions to reduce prescription opioid abuse had a moderate or large effect on preventing patients' clinically appropriate access to pain treatment.

Conclusions: Although physicians are unaware of some facets of opioid-related morbidity, most support a variety of clinical and regulatory interventions to improve the risk-benefit balance of these therapies.

807. The Combination Tenofovir/Lamivudine (Emtricitabine)/Efavirenz (Nevirapine) Better Tolerated Than Zidovudine/Lamivudine/Nevirapine in a Prospective Observational Study of Adverse Effects in Newly Treated Individuals in Burkina Faso

Frank ER Zongo, Emile Ouedraogo, Souleymane Fofana, Arsène Zongo, Arsène Ouedraogo, Moussa Ouedraogo.

Axe Santé des Populations et Pratiques Optimales en Santé, Centre de Recherche du Centre Hospitalier Universitaire (CHU) de Québec, Québec, QC, Canada; Faculté de Pharmacie, Université Laval, Québec, Canada; Centre National de Vigilance des Produits de Santé, Ministère de la Santé, Ouagadougou, Burkina FASO; Unité de Formation et de Recherché en Sciences de la Santé, Université de Ouagadougou, Ouagadougou, Burkina FASO; WHO Country office, World Health Organization, Ouagadougou, Burkina FASO.

Background: The marketing generic antiretroviral has improved access to treatment in developing countries. However, drug tolerance during post marketing stage is unknown because of weak national drug monitoring systems.

Objectives: To describe adverse effects of antiretroviral treatment and to explore the factors associated with effects during post marketing stage.

Methods: A cohort, prospective, multisite and observational study using data from 334 adult patients with HIV was conducted in three public hospitals involved in Burkina Faso HIV care program from January 2013 to March 2014. Patients were followed up during 6 months after antiretroviral treatment.

The patients initiating a first-line treatment protocol (including zidovidune or tenofovir or abacavir+ lamividune or emtricitabine+ efavirenz or nevirapine or boosted lopinavir) were selected. The first antiretroviral adverse effect was identified after causality assessment (WHO method).

Cox regression models were used to identify factors associated with adverse effects. Adjusted hazard ratios (aHR) and 95% confidence intervals were estimated.

Results: The cohort was aged 39.0 ± 9.0 on average. Adverse effects were observed in 23.1% of individuals. Among them, 7.8% had a serious adverse effect and effect was unexpected in 18.2%. Blood cells and gastro intestinal system were most affected (15.9% and 4.8% of the cohort).

Patients over 40 years were more likely to have adverse effect compared with those aged ≤40 years (aHR = 1.66; 95%CI = 1.04–2.67). When compared to those using zidovudine + lamivudine + nevirapine (the most prescribed protocol), individuals using other protocols were 51% (tenofovir + lamivudine (emtricitabine) + efavirenz) and 52% (tenofovir + lamivudine (emtricitabine) + nevirapine) more likely to avoid adverse effect (aHR = 0.49; 95% CI = 0.26–0.94 and aHR = 0.48; 95%CI = 0.24–0.94, respectively).

Conclusions: Age and antiretroviral treatment were associated with incidence of adverse effect. Some antiretroviral combinations would be preferred for initiation of treatment because of their best tolerance.

808. ECG Monitoring of Hospitalised Patients Using Domperidone, Before and After Media Attention Regarding Sudden Cardiac Death

Selma Saaid,[1] Matthijs L. Becker,[2] Teun van Gelder,[3] Patricia MLA van den Bemt.[3] *[1]Utrecht University, Utrecht, The Netherlands; [2]Pharmacy Foundation of Haarlem Hospitals, Haarlem, The Netherlands; [3]Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam, The Netherlands.*

Background: In March 2013, Dutch media paid much attention to the antiemetic domperidone, which was claimed to have caused 10 deaths in the Netherlands because of its QTc prolonging effect.

Objectives: To determine the effect of the media attention on ECG monitoring by physicians of hospitalised patients using domperidone and the effect on physicians' prescribing behavior.

Methods: Design: a two center, retrospective cohort study

Study population and setting: Two cohorts of domperidone users were included from both an academic and a general teaching hospital. The first cohort included patients whose domperidone treatment was initiated between 1 February 2012 and 12 March 2013('before-period') and the second cohort between 14 March 2013 and 1 April 2014 ('after-period').

Main outcomes: Primary outcome was the proportion of domperidone users with one or more ECG recordings before (90 days or less) or during domperidone treatment. Secondary outcomes were the proportion of domperidone users with an ECG recording both before and during treatment, and the proportion of patients with an ECG recording only during treatment. Exploratory outcome was the proportion of domperidone prescriptions of all antiemetic prescriptions.

Statistical analysis: Relative risks and 95% confidence intervals were calculated.

Results: A total of 460 patients were included. Patient characteristics were comparable between both periods. The primary outcome was 52.3% in the before-period and 56.0% in the after-period (RR 1.07, 95%CI 0.90–1.27). Secondary outcomes did not show any significant differences either (1.16 (0.69–1.93) and 1.32 (0.85–2.06)). After stratifying per hospital, no significant differences were found. A decrease in domperidone prescription from 6.5% to 2.6% was found for the academic hospital (0.40 (0.35–0.45)). For the general hospital, the change from 1.1% to 1.2% was not statistically significant.

Conclusions: The media attention of March 2013 did not change ECG monitoring by physicians of domperidone users. In the academic hospital, the media attention was followed by a decrease in prescription rates. In the general hospital, no change in prescribing was found.

809. Application of Quantitative Methodologies for Benefit-Risk Assessment: Case Study with Rosiglitazone and Pioglitazone

Diogo Mendes,[1,2] Carlos Alves,[1,2] Francisco Batel Marques.[1,2] *[1]Central Portugal Regional Pharmacovigilance Unit (UFC), Centre for Health Technology Assessment and Drug Research (CHAD), AIBILI, Coimbra, Portugal; [2]School of Pharmacy, University of Coimbra, Coimbra, Portugal.*

Background: The debate on the cardiovascular safety (CV) of rosiglitazone has been intense since the publication of Nissen and Wolski' meta-analysis. Based on the same evidence, two drug agencies made contradictory regulatory actions. While EMA decided to withdraw rosiglitazone, FDA kept the drug in the market and further recently voted to ease the current restrictions. This case highlights the need for investigating benefit-risk (B/R) assessment methodologies.

Objectives: To assess the B/R ratios of rosiglitazone and pioglitazone in the treatment of type 2 DM by weighting efficacy and safety using metric indices.

Methods: Data were retrieved from clinical trials identified from a FDA Rosiglitazone and Pioglitazone Meta-Analyses and manufacturers' registries. Data analyses were stratified according to different comparators and background therapy. NNT and NNH values were estimated for efficacy (proportion of HbA1c responders) and safety (CV events, CVD and all-cause death). LHH values were calculated as the ratio NNH/NNT.

Results: Statistically significant NNT values were found for rosiglitazone versus any comparator except from sulfonylurea and pioglitazone versus comparators. Statistically significant estimations were obtained for rosiglitazone versus placebo on MIF (NNH = 500; LHH = 125), serious myocardial ischemia (MIS) (NNH = 227; LHH = 57), total MIS (NNH = 152; LHH = 38), and congestive heart failure (CHF) (NNH = 260; LHH = 65); rosiglitazone + insulin versus

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comparators on CVD (NNH = 255; LHH = 51), serious MIS (NNH = 91; LHH = 18), total MIS (NNH = 66; LHH = 13), and CHF (NNH = 79; LHH = 16); pioglitazone versus sulfonylurea on CHF (NNH = 105; LHH = n.a.); pioglitazone + metformin versus comparators on MIF (NNH = 182; LHH = 46), serious MIS (NNH = 122; LHH = 31) and total MIS (NNH = 85; LHH = 22); and pioglitazone + insulin versus comparators on CHF (NNH = 43; LHH = n.a.).

Conclusions: The divergent actions taken by FDA and EMA, as well as the NNH and LHH values obtained for rosiglitazone and pioglitazone preclude definitive conclusions about a threshold that could support withdrawal decisions. The utility of quantitative methodologies to support regulatory decisions deserves further investigation.

810. Benefit-Risk Assessment of Statins: A Multiple Criteria Decision Analysis

Hsing-Chun Hsieh,[1] Jason C. Hsu,[1] Yea-Huei Kao Yang,[1] Christine Y. Lu.[2] *[1]School of Pharmacy and Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA.*

Background: Hypercholesterolemia is one of the major modifiable risks of coronary heart disease, which is one of the leading causes of death in the developed countries. Statins (HMG-CoA reductase inhibitors) are the most common lipid-lowering medications for treatment of hypercholesterolemia.

Objectives: To quantitatively evaluate the efficacy and safety of statins among the general population using an integrated assessment method.

Methods: We used multiple criteria decision analysis (MCDA) method to assess the benefits and risks of six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin). The MCDA models contained multiple criteria for benefits (reduction of low density lipoprotein cholesterol, prevention of major coronary events, prevention of major cerebrovascular events, and prevention of cardiovascular deaths) and risks (risk of myalgia/myopathy, risk of liver injury, risk of incident diabetes, and risk of other adverse events). We pulled data from the literature on effect sizes (with 95% confidence intervals) for benefit and risk criteria for each drug compared with other drugs. A performance score for each statin that combined all of its sub-criteria of benefits and risks and their weights, relative to other agents, was calculated.

Results: Our findings showed that "fluvastatin" had the highest overall performance score among all medications. In order of performance scores: fluvastatin (0.672), simvastatin (0.651), lovastatin (0.586), rosuvastatin (0.553), pravastatin (0.527), and atorvastatin (0.519). Fluvastatin had the highest score for benefits (0.585) among all agents and pravastatin had the highest score for risks (0.268). Sensitivity analyses of the uncertainties of criteria weights suggested that our results were robust.

Conclusions: This study applied the MCDA method to assess different treatments and made explicit the preferences and trade-offs between multiple criteria and suggested that fluvastatin might be preferred over other statins for general population. Our study not only ranked drugs by performance scores based on their risk-benefit balance but also compared drugs' effects on specific benefit and risk criteria.

811. Preferences of Diabetes Patients for Lipid-Lowering Treatment: A Discrete Choice Experiment

Dianna de Vries,[1] Sieta T. de Vries,[1] Petra Denig.[1] *[1]Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands.*

Background: Lipid-lowering treatment is recommended for almost all diabetes patients. However, high non-adherence and discontinuation rates are a problem in clinical practice. It is expected that age influences the preferences for this treatment.

Objectives: The aim of this study was to assess whether age influenced (1) the willingness of diabetes patients to continue using lipid-lowering treatment and (2) the importance of specific drug characteristics.

Methods: Patients being prescribed at least one oral glucose-lowering drug and one lipid-lowering drug completed a questionnaire including a discrete choice experiment. Patients needed to imagine that their lipid level was too high, and choose between two hypothetical lipid-lowering drugs and the option to stop lipid-lowering treatment. Options differed in their effect on cholesterol level, risk of death, risk of limitations due

to heart attack, risk of limitations due to stroke, risk of adverse events and the intake moment. Multinomial logit models were used to assess the importance attached to the treatment characteristics. Responders who failed a dominant choice set were excluded.

Results: Of 899 patients contacted, 251 responded and 203 completed the questionnaire. We excluded 20 responders for failing the dominant choice and eight patients who did not fulfil the inclusion criteria, resulting in 175 patients in the analysis (19% ≥75 years; 59% male). Only seven patients considered for one or more choice sets to stop lipid-lowering treatment, which was not affected by age. When choosing between treatments, the effect on the risk of death ($p=0.001$) was considered less important and adverse events ($p\leq0.001$) more important with increasing age.

Conclusions: Elderly diabetes patients who are using lipid-lowering drugs are equally willing to continue such treatment when their cholesterol level is too high as younger patients. The finding that younger patients placed more emphasis on preventing death and less on the risk of adverse events might suggest that these patients are more willing to be treated with higher dose of lipid-lowering treatment when needed.

812. Development of a Shared Decision-Making Tool to Assist Patients and Clinicians with Assessing the Individualized Risks and Benefits of Oral Anti-Coagulation Therapy for Atrial Fibrillation

Karen Kaiser,[1] Wendy Cheng,[2] Sally Jensen,[1] Marla Clayman,[3] Frances Schwiep,[2] Andrew Thappa,[2] Anita Chawla,[4] Jeffrey J. Goldberger,[5] Nananda Col,[6] Jeff Schein.[7] *[1]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Analysis Group, Inc., Boston, MA, USA; [3]American Institutes for Research, Chicago, IL, USA; [4]Analysis Group, Inc., Menlo Park, CA, USA; [5]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [6]Shared Decision Making Resources, Georgetown, ME, USA; [7]Janssen Scientific Affairs, LCC, Raritan, NJ, USA.*

Background: The 2014 AHA/ACC/HRS guideline for managing atrial fibrillation (AF) encourages clinicians to partner with patients to discuss the benefits and risks of treatment and patient concerns, yet few tools facilitate these kinds of discussions.

Objectives: To develop an interactive shared decision-making (SDM) tool that provides patient-specific information about the risk-benefit tradeoff of oral anticoagulants (OACs) and integrates these risks with patient preferences to enhance clinician-patient dialogue about treatment decisions.

Methods: A comprehensive literature review and input from experts in AF, SDM, and risk communication informed the study. After discussions with experts, we identified the best risk prediction models for stroke ($CHADS_2$ index) and major bleeding (ATRIA index). We extracted factors most important in choosing treatment through four patient focus groups and eight interviews with clinicians, and used these to inform the design and assessment of patient preferences. We integrated the risk prediction models with preference domains to develop a prototype of the AF SDM tool. We then evaluated the tool for clarity and usability through patient cognitive testing.

Results: Our design had four modules: (1) understanding AF and its relationship to stroke and bleeding risk; (2) stroke risk assessment; (3) bleeding risk assessment; and (4) patient preference assessment. Graphics were developed to enhance understanding of the stroke/bleeding risk indices; interactive risk calculators were included to compute patient-specific stroke and bleeding risks. Key modifications from cognitive testing included improvements on the intelligibility and clarity of graphics and text. The final tool calculates the patient-specific risks and benefits of OACs and couples it to patient preferences to assist patients in decision making.

Conclusions: The AF SDM tool can help patients and their clinician choose the best treatment for their individual risks and preferences and represents a new approach to educating patients on the benefits and risks of OACs.

813. Benefit-Risk Assessment of Nonprescription Diclofenac

Eric P. Brass,[1] Jessica Swanson,[2] Steven M. Weisman.[2] *[1]Harbor-UCLA Center for Clinical Pharmacology, Harbor-UCLA Medical Center, Torrance, CA, USA; [2]Innovative Science Solutions, Morristown, NJ, USA.*

Background: Nonprescription (NP) marketing status facilitates consumer access to effective drugs. However, NP status may be associated with differential

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risks and benefits when compared to prescription-only (P) access due to how consumers elect to use the drug in the unsupervised NP setting. Formal benefit-risk tools may allow a more complete assessment of existing and proposed NP drugs.

Objectives: The current work was undertaken to provide a structured benefit-risk assessment of low dose (less than or equal to 75 mg) oral NP diclofenac versus P diclofenac.

Methods: The Benefit-Risk Assessment of Nonprescription Drugs (BRAND) tools were used. The BRAND tools consist of a modified value-tree and a semi-quantitative scoring tool based on multi-criteria analysis principles. The value-tree was populated using solicited expert opinion and literature sources. The scoring tool was completed based on literature data.

Results: The value-tree exercise identified potential benefit attributes for oral NP diclofenac based on comparison of outcomes with alternative consumer treatment decisions (no-treatment, other NP drug, and P diclofenac). Examples of potential benefit attributes included improved pain relief, lower gastrointestinal risk and decreased hepatotoxicity versus other treatment options. Similarly, potential risk attributes included increased cardiovascular (CV) events, and increased renal, heart failure, and gastrointestinal (GI) events, particularly if used by high-risk cohorts. The scoring tool assessed the frequency and clinical impact of each attribute identified and cited the data sources forming the scoring justifications. For several potential attributes, data were not available to provide a robust score. Overall, the scoring identified important benefits of oral NP diclofenac driven by comparative efficacy or safety versus other treatments. Differentiating risks were also present, and the scoring matrix identified where risk mitigation could meaningfully impacts benefit-risk considerations.

Conclusions: Oral NP diclofenac has the potential to yield net benefit if risk mitigation strategies minimize use by individuals with high risks of CV, GI or renal adverse events.

814. Defining Risk Profiles in Special Populations – Results from a Post Authorisation Safety Study (PASS) of Seroquel XL© Conducted in Primary Care in England

Deborah Layton,[1,2] Vicki Osborne,[1,2] Miranda Davies,[1,2] Saad Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK;. [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK.*

Background: A Risk Management Plan developed for quetiapine extended release (Seroquel XL©), included a PASS to examine its safety and use as prescribed in primary care. Objectives include exploring risks in special populations (SP).

Objectives: To describe risk profiles by SP groups (indication, past medical (pmh) history, prior psychoactive drugs, and age >65, <64)

Methods: An observational, single-exposure cohort design. Data were derived on exposure from dispensed prescriptions; on events from forms completed by physicians 12 months (m) post first exposure. For general surveillance crude incidence densities (ID) per 1000 pt-m were calculated for events in m1, 2–6, 7–12 and 1–12 for cohort, and by SP group. Overdose events were grouped by suicidal ideation (SI), suicidal behaviour (SB), self-injurious behaviour (SIB). Event ID differences ($IDD_{1–2–6}$) + 95%CI excluding the null (0) were signals of starting treatment. Survival methods estimated rates of overdose and hyperglycaemic (HG) events (+95%CI) per 1000 pt-m (where $n > 7$ and excl pts if event date missing).

Results: Cohort = 13 276; 59% were female; median age 43 years (IQR 33, 55). Events with highest $ID_{1–12}$ were as follows: sedation, $n = 317$: ID 40; somnolence, $n = 288$: ID 47; and weight increased, $n = 198$: ID 54. Somnolence amd sedation were associated with starting treatment overall ($IDD_{1–2–6}$:3.8(1.5, 5.7) and 2.5(0.8, 4.2), respectively) and in SP groups: indication bipolar disorder or non-licensed indications; age ≤64 years; and pmh depression. For HG events, the highest rates $m_{1–12}$ were raised random blood sugar ($n = 122$):1.0 (0.8, 1.2) and raised fasting plasma glucose ($n = 104$):0.8 (0.7, 1.0). SP groups with pmh IGT and diabetes appeared to have highest rates. Of 104 overdose events, pmh mental illness was reported for all pts; event rates $m_{1–12}$ were as follows: SB ($n = 84$):101.8 (82.2, 126.1), SI ($n = 1$):4.0 (0.6, 28.4), and SIB ($n = 15$): 36.6 (22.0, 60.1).

Conclusions: For frequently reported central nervous system, psychiatric and HG events, many pts had pre-existing risk factors that are likely to put them at elevated risk. This study demonstrates the ongoing importance of observational studies to support the risk: benefit evaluation of medications.

815. U.S. Women Who Could Benefit from Tamoxifen or Raloxifene for Breast Cancer Chemoprevention in 2010

Andrew N Freedman,[1] Donna R. Rivera,[1] Mitchell H. Gail,[1] Barry I. Graubard.[1] *[1]National Cancer Institute, Rockville, MD, USA.*

Background: The U.S. Food and Drug Administration (FDA) has approved two drugs for breast cancer (BC) chemoprevention: tamoxifen for women aged 35 years or older and raloxifene for postmenopausal women. Both medications require a 5-year invasive breast cancer risk of 1.67% or higher for clinical use. While BC trials have demonstrated both tamoxifen and raloxifene reduce risk of invasive breast cancer (IBC), these agents have been associated with potential adverse outcomes.

Objectives: We compare the number of U.S. women who would be eligible for tamoxifen and/or raloxifene chemoprevention, with the number of women who have evidence of a positive benefit/risk index for these drugs. These data assist in evaluating the potential public health impact of breast cancer chemoprevention and may help identify subgroups of U.S. women who would especially benefit.

Methods: We used nationally representative weighted data from the 2010 National Health Interview Survey (NHIS) Cancer Control Module to estimate the total number of U.S. women, aged 35–79 years who were eligible for tamoxifen chemoprevention and those women aged 50–79 years eligible for raloxifene chemoprevention. We then estimated ethnic differences among women with a positive benefit/risk chemoprevention index.

Results: There are 14 232 626 (19.2%, 95%[CI] = 18.2–20.1%) women aged 35–79 years, without BC, in 2010, eligible for tamoxifen and 13 300 080 (30.9%, 95%CI = 29.4–32.5%) women aged 50–79 years, would be eligible for raloxifene. Ethnic differences indicate White women had the highest percentage eligibility, while smaller numbers of Black and Hispanic women demonstrated a positive benefit/risk index.

Conclusions: A substantial percentage of U.S. women would be eligible for BC chemoprevention according to FDA approved indications, though a smaller percentage would have an estimated net benefit. However, for postmenopausal women (aged 50–79 years), 3.5 times as many women (2.5 million) would have an estimated net benefit for raloxifene than for tamoxifen, due to raloxifene's better benefit/risk profile.

816. Qualitative Research with Primary Care Clinicians and Neurologists Regarding Drug Safety Communications

Suzanne L. West,[1] Craig Lefebvre,[1] Lauren A. McCormack,[1] Olivia Taylor,[1] Paula Rausch.[2] *[1]RTI International, Research Triangle Park, NC, USA; [2]Division of Health Communications, US Food and Drug Administration, Silver Spring, MD, USA.*

Background: Continuing postmarket surveillance and risk assessment are important to identify adverse events not apparent during drug development. Hence, clinicians are challenged to stay current with the newest drug safety information released by the US FDA and other sources. Clinicians need current drug safety information to discuss the benefits and risks of drugs with their patients.

Objectives: The goals of this study were to determine how clinicians learn about new drug safety information and to understand how typical benefit-risk communications occur during a patient visit.

Methods: We conducted an innovative qualitative study with neurologists and family practice physicians (FPPs) to assess which resources they use to obtain postmarket safety information, their thoughts on FDA's communications and to explore the provider-patient dialog regarding the benefits and risks of medications. The study used several design research probes in a 2-h session held with neurologists attending a regional clinical symposium and telephone interviews with FPPs identified via the American Association of Family Practitioners. All analyses were descriptive to examine common themes and patterns in the qualitative data.

Results: We obtained input from 21 neurologists and nine FPPs. Neurologists and FPPs noted many different sources for staying current on postmarket drug safety information but almost all relied on journal articles and FDA communications. How clinicians handle new safety warnings depends on the importance of the drug to their patient population and their own weighing of the risks and benefits. Clinicians find that some patients are very interested in hearing about drug

side effects; others never ask about side effects. Although clinicians warn not to do so, they still find their patients discontinue their drugs when they hear about serious side effects from the news media or other sources.

Conclusions: Neurologists and FPPs need easy access to clinically relevant and concise post-marketing safety information from credible sources. Quick access to benefit and risk information may lead to improved patient engagement regarding drug prescribing during the clinical encounter.

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817. Disproportionality Analysis of Cardiac Arrhythmia Events in the FDA Adverse Event Reporting System for Buprenorphine Patch

Nelson E. Sessler,[1] Ekaterina Walker,[1] Paul M. Coplan.[1] [1]*Risk Management and Epidemiology, Purdue Pharma L.P., Stamford, CT, USA.*

Background: The buprenorphine transdermal delivery system/patch (Butrans®) is indicated for use in the USA at doses of 5, 7.5, 10, 15, and 20 mcg/h for the treatment of chronic pain. Maximum indicated dose of 20 mcg/h was due to the prolongation of QTc interval observed in clinical trials of healthy volunteers at doses ≥40 mcg/h. Sublingual buprenorphine tablets and film (Suboxone®/Subutex®) are indicated for opioid dependence maintenance therapy and when administered at recommended target dose of 16 mg/day provide fivefold greater relative systemic exposure of buprenorphine as compared to Butrans 20 mcg/h.

Objectives: This study assessed if there was disproportional reporting of clinical cardiac arrhythmia events in FDA's Adverse Event Reporting System (FAERS) relative to other events in the database for buprenorphine sublingual tablet/film and patch. Methadone, an opioid with clinically documented association with cardiac arrhythmia events was used as comparator.

Methods: Clinical cardiac arrhythmia was assessed in FAERS using the Standardized MedDRA Query (SMQ) for Torsade de Pointes (TdP) and/or QT Prolongation (QTP). Multi-item gamma Poisson shrinker (MGPS) algorithm was applied to extracted FAERS data to generate empiric Bayes geometric mean (EBGM) values with corresponding confidence intervals (CIs). Lower 95%CI limit of EBGM >2 was used as standard measure of an increase in disproportionality.

Results: Methadone was associated with disproportionately increased reporting rates for TdP/QTP (EBGM 4.92, 95%CI: 4.70–5.15). Buprenorphine products were not associated with signal of disproportionate reporting for TdP/QTP: buprenorphine transdermal (EBGM 1.76, 95% CI: 1.28-2.38), buprenorphine/naloxone sublingual (EBGM 1.65, 95%CI: 1.49–1.83), and buprenorphine sublingual (EBGM 0.78, 95%CI: 0.62–0.97). Similar results were observed in subsets of gender and age.

Conclusions: Adverse event reporting for cardiac arrhythmia events was disproportionally increased for methadone, but not for buprenorphine patch or for buprenorphine sublingual tablet/film that provides several-fold higher daily systemic exposure to buprenorphine than the patch.

818. What Can Social Media Networks Contribute To Medicines Safety Surveillance?

Preciosa M. Coloma,[1] Benedikt Becker,[1] Miriam C.J. M. Sturkenboom,[1] Erik M. van Mulligen,[1] Jan A. Kors.[1] [1]*Medical Informatics, Erasmus University Medical Center, Rotterdam, South Holland, The Netherlands.*

Background: There is growing interest in whether social media can capture patient-generated information relevant for pharmacovigilance that cannot be found in traditional sources.

Objectives: To evaluate the potential contribution of mining social media networks for medicines safety surveillance using examples of drug-adverse event associations that have been flagged as potential safety signals: (1) rosiglitazone and cardiovascular (CV) events and (2) human papilloma virus (HPV) vaccine and infertility.

Methods: We collected publicly accessible posts on Facebook, Google+, and Twitter from as far back as

possible until September 2014 using their respective search application programming interfaces. For each use case, data were queried for co-occurrence of keywords related to the drug/vaccine of interest and the event of interest within a post. Messages were analysed with respect to geographical distribution, context, sentiment and linking to other web content. We manually reviewed all posts for personal accounts of adverse drug experience.

Results: A total of 2537 posts related to rosiglitazone/CV events and 2135 posts related to HPV vaccine/infertility were retrieved, with majority of posts representing data from Twitter (98% and 87%, respectively) and originating from users in the USA. Almost 25% of rosiglitazone-related posts contained links to other web pages, mostly news items, followed by law firms' advertisements and blogs. 7Seventy-five percent of HPV vaccine-related posts referenced other web pages, mostly blogs. Sentiment analysis showed predominantly affirmation of the association between rosiglitazone and CV events (72%, $n = 1821$), and that of HPV vaccine and infertility (82%, $n = 1753$). There were only 10 posts describing rosiglitazone/CV adverse event experiences, while there were nine posts describing HPV vaccine-associated problems related to infertility.

Conclusions: Current publicly available data from social media networks are sparse, incomplete, and largely untrackable for the purpose of providing early clues of safety concerns. The potential value of mining data from social networks appears to be greater for measuring awareness and public sentiment regarding emerging safety issues.

819. The Use Off-Label of Thalidomide in Brazil from 2010 to 2014

Nair R. Souza,[1] Francisco J.R. Paumgartten.[1] *[1]HEA, ENSP - FIOCRUZ, Rio de Janeiro, Brazil.*

Background: Although thalidomide was banned in almost all countries in mid-1960s, the use of thalidomide has never been completely discontinued in Brazil. Owing to its efficacy to treat ENL, and the high prevalence of Hansen disease, in Brazil, thalidomide is listed as an essential drug. In 2011, a new regulation on thalidomide control was put into effect by Brazilian Health Surveillance Agency (ANVISA). Overall, the new regulation made control on dispensing and prescription apparently more efficient and established rules to authorize thalidomide dispensing if it is prescribed for an off-label indication. In this study, we report and analyze data on off-label indication of Thalidomide in Brazil, before (2010) and after (2012–2014) new regulation.

Objectives: The data were used to identify prevalence, determinants and spectrum of off-label thalidomide after established new rules for the use off label indication of Thalidomide.

Methods: Retrospective study. Our data are based from the files found in ANVISA.

Results: Our findings identified the number of patients making use of use off-label indication thalidomide increased almost 94% of 171 patients in 2010 before the regulation to 323 patients in 2012, keeping it at around 300 patients by the end of 2014. They received together a total of 24 129 tablets of 100 mg each) during the first year of new rules enforcement. Myelodysplastic syndrome accounted for over 20% of all prescriptions in both time periods analyzed in this study. During 5 years, off-label thalidomide was dispensed to 662 women, around 24% were between 15 and 49 years old, an age group defined by WHO as that of generally fertile women. São Paulo, Minas Gerais and Rio de Janeiro were the provinces more prescribed for an off-label indication.

Conclusions: The data demonstrate the increased consumption of the off-label use thalidomide. The majority are patients with serious diseases, possibly terminals, which are particularly vulnerable individuals. Future research into off-label thalidomide use should focus on the most appropriate strategies for monitoring the use off-label in the country.

820. Can Online Data Lead To the Earlier Detection of Drug-Related Adverse Events?

Mei S Duh,[1] Pierre Cremieux,[1] Marc Van Audenrode,[2] Francis Vekeman,[2] Paul Karner,[1] Haimin Zhang,[2] Paul Greenberg.[1] *[1]Analysis Group, Inc., Boston, USA; [2]Group d'analyse, Ltée, Montreal, Canada.*

Background: There is interest in utilizing online data for pharmacovigilance. Few studies have examined the potential for such data to lead to the earlier detection of drug-related adverse events (AEs) compared with conventional pharmacovigilance data sources such as US FDA MedWatch (MW).

Objectives: To compare the patterns of AE data from AskaPatient.com (ASK), a popular online health forum, with MW for two drugs: atorvastatin (AT) and sibutramine (SB).

Methods: We extracted web postings on ASK for AT and SB from 2001 to 2014. For each drug, we compared the demographic characteristics and frequencies of the most commonly mentioned AEs, and well-known AEs associated with these drugs (AT: muscle pain; SB: CV issues), with AE reports from MW through 2013. Using Granger causality tests, we also assessed whether ASK postings predicted MW reports for the well-known AEs.
Results: ASK contained 998 postings for AT and 270 for SB. MW contained 58 377 reports for AT and 7332 for SB. While similar shares of MW and ASK patients were female, ASK patients were significantly younger (mean age, AT: 60.1 years vs. 53.9 years; SB: 43.7 years vs. 36.8 years; $p < 0.001$ for both). For both drugs, several top AEs in ASK were also top AEs in MW, but ASK reports were more concentrated on similar types of AEs (share of reports comprised by the top 10 AEs, MW vs. ASK: AT, 45.7% vs. 88.7%; SB, 52.3% vs. 85.9%). Compared with MW, fewer serious AEs were reported in ASK (AT, pain: 39.3% vs. 2.5%; SB, CV issues: 62.5% vs. 7.9%; $p < 0.001$ for both). ASK reports tended to focus on quality of life-related AEs. For SB, time series of ASK postings of cardiac AEs trailed MW reports for cardiac AEs 4 months later (Granger causality test $p = 0.045$). For AT, there was no Granger causality between ASK and MW.

Conclusions: AE reports examined for AT and SB from ASK and MW suggest that web reporters are younger and focus on fewer and less serious AEs compared with patients whose AEs are reported in MW. For specific AEs, online sources may give earlier indications of AEs compared with MW. However, as with MW data, higher-quality data sources and appropriate methods are needed to properly evaluate these hypothesis-generating drug safety signals.

821. Reasons for and Time to Antipsychotic (AP) Treatment Discontinuation: Results from a Post-Authorisation Safety Study

Deborah Layton,[1,2] Vicki Osborne,[1,2] Miranda Davies,[1,2] Saad A.W. Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, Hampshire, UK; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, Hampshire, UK.*

Background: APs are generally effective, but some patients (pts) may stop soon after starting due to poor tolerability. Quetiapine prolonged-release (Seroquel XL©) was developed to improve tolerability and administration via once-daily dosing. The Risk Management Plan had a requirement to describe utilisation and monitor safety as prescribed to new XL users in primary care, via Modified Prescription-Event Monitoring (MPEM).

Objectives: A post hoc analysis to describe common factors associated with stopping XL.

Methods: MPEM uses an observational cohort design. Questionnaires completed by physicians (GPs) collected data on pt demographics, prior medical history (pmh), prior/current medication use, XL exposure and events (incl. reasons for stopping (RFS)) September 2008 to February 2013. Descriptive statistics described the cohort. Kaplan–Meier methods analysed time to stopping in the first 12 months after starting. Crude Odds ratios (OR) and 95%CI) were calculated to explore relationships between stopping and pt characteristics

Results: Cohort = 13 276; 59% (7828) female; median age 43 years (IQR 33, 55); indication: Bipolar disorder (30%, 3820), major depressive disorder (22%, 2844), schizophrenia (18%, 2373) and other non-licensed (29%, 3750). A total of 3753 pts (28% cohort) stopped treatment (10% by day 56; 25% by day 220). There was significant variation by indication (Log rank test $p < 0.001$) – pts with other non-licensed indications were most likely to stop (31%, 1162). The most frequent non-clinical and clinical RFS were the events: 'drug ineffective' (19%, 581/3094) and 'sedation' (15%, 269/750). Pts with a pmh somnolence/sedation versus those without were more likely to stop due to sedation: OR 3.3 (2.1, 4.9). Naive AP use, a pmh of extrapyramidal symptoms, metabolic syndrome, diabetes, and impaired glucose tolerance appeared to be risk factors for stopping for any reason.

Conclusions: In this study, nearly one third of pts stopped Seroquel XL© <12 months and RFS were varied. Certain pt characteristics may also be associated with a higher risk of stopping. Further work will explore the impact of dosing. This data can help support GPs decisions on prescribing and management to prevent premature treatment cessation.

822. Direct Healthcare Professional Communications – Can Their Effectiveness Be Measured?

Taco Monster,[1,2] Liana Martirosyan,[1] Peter Mol.[1,2] *[1]Dutch Medicines Evaluation Board, Utrecht, The Netherlands; [2]Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

Background: Direct Healthcare Professional Communications (DHPCs) are an important tool for regulatory agencies to communicate important risk information related to drug use. Their effectiveness is not well known beyond impact on total drug use.

Objectives: This study aims to classify the type of problems and recommendations in DHPCs issued in the EU and to assess the feasibility of quantifying the recommended actions in existing electronic healthcare databases (EHDs).

Methods: All DHPCs issued in the EU between 2011 and 2013 were reviewed. For each DHPC, the type of problem addressed and subsequent recommendations were categorised by two researchers using a pre-existing classification form. Subsequently, the measurability of intended effects in EHDs registered at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance was assessed.

Results: Between 2011 and 2013, 112 DHPCs were issued. Most warned about adverse drug reactions (61%) or production problems (21%), and almost all (95%) recommended a change in prescribing behaviour. For 38% of the DHPCs, the effect of at least one recommendation can be measured using pharmacy dispensing databases (e.g. dose change and no prescribing in case of drug-drug interaction). Most DHPCs (69%) contained recommendations (e.g. contraindications) that would require additional information on diagnoses or other patient characteristics from EHDs to measure intended effects. The effect of 38% of DHPC recommendations would require laboratory or physical examination data. Nine DHPCs (8%) communicated safety information without specific recommendations, and their effectiveness can only be measured through a survey or protocol review.

Conclusions: The effectiveness of most DHPCs can be measured in existing EHDs, although for some DHPCs, suitable EHDs may be only available in a few EU countries and especially laboratory and physical examination data may not always be available. Evaluation of the effectiveness of DHPCs is considered important, and therefore, standardised methods to measure the effectiveness of DHPCs that include recommendations on prescribing behaviour need to be developed.

823. Adverse Events in Patients with Advanced Non-Small Cell Lung Cancer – Findings from IMS Oncology, a US Oncology Electronic Medical Record (EMR) System

Lei Chen,[1] Belen San Antonio,[2] Jonathan Lucas Swain,[1] Lucy Mitchell,[3] William J John,[1] Hafida Arkoub,[4] James A Michael,[1] Dale Quentin Marmaduke,[1] Yuer Yan.[1] *[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Eli Lilly and Company, Madrid, Spain; [3]Eli Lilly and Company, Erl Wood, UK; [4]Eli Lilly and Company, Neuilly sur Seine, France.*

Background: Characterizing safety profiles is important to evaluate benefit-risk of new and existing therapies. The overall safety profile of systemic treatments in advanced non-small cell lung cancer (NSCLC) patients in real world settings is not well characterized, as population-based studies evaluating adverse events (AEs) in the Stage IIIB/IV NSCLC patients dated back to 2005, prior to approval of a number of new drugs and significant changes in medical guidelines.

Objectives: To describe systemic treatment use and AEs for Stage IIIB/IV NSCLC patients diagnosed in 2004–2012, using a US community-based oncology practice EMR system.

Methods: Medical records were evaluated for stage IIIB/IV NSCLC patients in the IMS Oncology database. Incidence of AEs during 3 and 6 months after the systemic treatment initiation were calculated. Baseline clinical characteristics were assessed by systemic treatment use. Analyses were further stratified by age.

Results: Of 7956 eligible patients, 3998 received systemic treatments and 3958 did not have any systemic treatment records. The most commonly recorded AEs during 3 months after treatment initiation were anemia, neutropenia, vomiting and dehydration. Incidence proportions of the AEs were higher in patients aged <70 years (e.g. anemia: 23% vs. 15%), while incidence rates were higher in patients aged ≥ 70 years (106/100 person-years [py] vs. 122/100 py). The pattern remains during 6 months after treatment initiation. Compared to those without systemic treatment records, among patients receiving treatments, there were more males (57% vs. 53%), age <70 years (67% vs.

59%), and exhibiting comorbidities such as CVDs (11% vs. 6%), hypertensive disease (15% vs. 9%), and COPD (7% vs. 3%).

Conclusions: The study generated important information about the AEs occurring in a representative community population who received systemic treatment for advanced NSCLC. The overall safety profile is helpful in assessing benefit risk of treating NSCLC patients in the real world. Future examination of survival benefit for this patient population is warranted to achieve a more complete understanding of the benefit-risk profile.

824. Pattern of Postmarket Requirements and Commitments and FDA Approval of Novel Therapeutic Agents from 2003 to 2013

Anura Deshmukh,[1] Andres Gomez,[1] Tzuyung D Kou.[1] *[1]Bristol-Myers Squibb, Pennington, NJ, USA.*

Background: Postmarket requirement and commitment (PMRC) are important activities that pharmaceutical companies conduct after drug approval to monitor safety or efficacy. Since The Food and Drug Administration Amendments Act of 2007, FDA has the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

Objectives: This study evaluated the feasibility of linking Drugs@FDA Database, PMRC database, and REMS status information into a master analytical dataset and explored potential association between PMRC and REMS.

Methods: Feasibility and longitudinal sectional analysis using publicly available FDA documents for all novel therapeutic agents approved between 2005 and 2012. The pattern of drug approvals with PMRC and REMS was compared between those in 2003–2007 and those after 2007.

Results: An entity relationship table was created to depict linkage between Drug@FDA and PMRC database. Between 2003 and 2007, the FDA approved 117 novel therapeutic agents for various indications. The average number of PMRC activity per drug approval between 2003 and 2007 was 2.83 (interquartile range, 2.48–3.11). Between 2008 and 2013, the FDA approved 167 novel therapeutic agents. The average number of PMRC activity per new drug approval was 3.68 (interquartile range, 3.35–4.17). Further evaluation of PMRC activities demonstrated an increase in the number of postmarket safety registry from 14 between 2003 and 2007 to 24 registry studies between 2008 and 2013. The number of pregnancy registry went from four between 2003 and 2007 to 18 between 2008 and 2013, and the cumulative number of drug approval with REMS requirement went from three in 2008 to 61 in 2013.

Conclusions: The preliminary findings demonstrated a temporal increasing in the average number of PMRC per NDA approval and an increase in the number of product safety registry studies. Additional analysis is needed to further describe any potential relationship between the application characteristics, the observed increase in PMRC, and the pattern of REMS requirement.

825. An Evaluation of Clinical Practices among UK General Practitioners in Managing Individuals Attempting to Quit Smoking with Varenicline

Muhammad Younus,[1] Kenneth R. Petronis,[1] Xiaofeng Zhou,[1] Harshvinder Bhullar,[2] Michelle Johnson,[2] Shobhna Koria,[3] Jingping Mo.[1] *[1]Epidemiology, Worldwide Safety and Regulatory, Pfizer Inc, New York, NY, USA; [2]Cegedim Strategic Data Medical Research Ltd, London, UK; [3]CSD THIN, London, UK.*

Background: Varenicline Summary of Product Characteristics (SmPC) was updated to include a warning on the potential risk of psychiatric symptoms with varenicline in February 2008.

Objectives: A survey was conducted to assess whether current clinical practices among UK general practitioners (GPs) in managing individuals attempting to quit smoking with varenicline are consistent with the updated SmPC.

Methods: A total of 1206 GPs that contribute data to The Health Improvement Network (THIN), a large primary care electronic database in the UK, were invited to participate in a self-administered survey.

Results: Of 1060 GPs who received the survey invitation, 786 (74.2%) responded to the survey. Consistent with the SmPC's instructions, most respondents (82%)

indicated that they asked or otherwise confirmed, either in all or in most patients, a history of any psychiatric disorder prior to prescribing varenicline during the year preceding the survey. The majority (66%) did not report that any of their patients had psychiatric symptoms during treatment with varenicline in the year preceding the survey. Of GPs who learned that (at least one of) their patients were experiencing psychiatric symptoms, the majority (85%) indicated that they immediately stopped varenicline, which is an appropriate action according to the SmPC, while 18% mentioned that they continued varenicline and observed their patients more closely, and 4% reported continued varenicline and observed their patients as before.

Conclusions: Overall, the survey data showed that the majority of GPs' self-reported prescribing practices in the year preceding the survey were in accordance with the varenicline SmPC's prescribing information.

826. Identifying Patients for Clinical Trials by Risk Stratification: The Case of an Intervention to Reduce Post-Operative Opioid Use in Total Joint Replacement

Jennifer L. Kuntz,[1] Eric S. Johnson,[1] Amanda F. Petrik,[1] Xiuhai Yang,[1] David H. Smith.[1] *[1]Kaiser Permanente Northwest Center for Health Research, Portland, OR, USA.*

Background: Opioid use after knee or hip replacement surgery is common; however, use more than 90 days post-surgery is defined as persistent and is a target for intervention.

Objectives: To develop a prediction model for persistent opioid use following replacement surgery that would improve the efficiency of patient identification for a clinical trial on opioid reduction.

Methods: We conducted a retrospective cohort study among Kaiser Permanente Northwest (KPNW) members who were aged >20 years and underwent knee or hip replacement surgery between 01/01/2010 and 31/12/2013. We followed patients for persistent opioid use, defined as an opioid refill 91 to 180 days following surgery. We used a stratified Cox regression model to synthesize a priori predictors into a persistent opioid use risk score that can be automatically calculated from electronic health record data. We then assessed the score's predictive ability.

Results: We identified 5635 knee and hip replacement patients. Of these, 35% of patients ($n = 1964$) persistently used opioids. The cumulative overall risk of persistent use was 35 per 100 patients (95%CI; 34.0, 36.5). The strongest pre-operative predictors were the number of morphine equivalents used, history of smoking, muscle relaxant or anticonvulsant use, and a substance abuse disorder diagnosis. The score explained 39.5% of the variation in persistent opioid use (95%CI; 37.2%, 41.8%) and successfully differentiated between patients who do and do not persist, with a C-statistic of 0.76. Enrolling patients in the trial based on predicted risk above the population median would result in the inclusion of 79% of all persistent-use patients.

Conclusions: The risk score's ability to discriminate between patients at highest and lowest risk for persistent opioid use makes it a useful tool for identifying patients who may most benefit from a post-operative opioid reduction intervention. Because the risk score targets high-risk patients, its use in our trial will increase efficiency in patient selection and statistical power. In turn, the number of patients that need to be enrolled and research costs is reduced.

827. Decrease in Diagnosed Abuse, Addiction, and Opioid Poisoning Among Patients Prescribed Opioids after Introduction of OxyContin with Abuse-Deterrent Characteristics

Aditi Kadakia,[1] Paul Coplan.[1,2] *[1]Department of Risk Management and Epidemiology, Purdue Pharma L. P, Stamford, CT, USA; [2]Department of Clinical Biostatistics and Epidemiology, University of Pennsylvania Perelman School of Medicine (Adjunct), Philadelphia, PA, USA.*

Background: Reductions in abuse of OxyContin after reformulation with abuse-deterrent characteristics were documented in substance abuse treatment, poison centers and abuser cohort populations but not yet among patients prescribed OxyContin.

Objectives: This study assessed the effect of abuse-deterrent characteristics of OxyContin on diagnosed abuse, addiction and opioid poisoning rates among patients prescribed opioids.

Methods: Rates per 100 person-years of diagnoses were calculated among individuals dispensed OxyContin or four comparator opioids prescribed in the MarketScan

commercial database. Time on opioid was calculated from dispensing records. Abuse was determined from ICD9CM 305.5x codes, addiction from 304.0x/304.7x, and poisoning from 965.00/965.02/965.09 codes. Changes in diagnoses rates from 1 year before to 1 year after reformulation were calculated.

Results: Diagnoses for opioid abuse/addiction/poisoning decreased −12% (95%CI: −17%, −7%) among all patients prescribed OxyContin, −29% (95%CI: −38%, −18%) among patients prescribed OxyContin alone and −10% (95%CI: −16%, −5%) among patients prescribed OxyContin concomitantly with other opioids. Changes for OxyContin alone (−29%) were significantly different from those for comparator opioids: rates increased 29% for ER oxymorphone, 8% for ER morphine, 15% for IR SE oxycodone, and 10% for IR hydromorphone. Among patients dispensed with multiple opioids concomitantly, the reduction for OxyContin was not significantly different from other opioids.

Conclusions: Significant decreases in abuse/addiction/poisoning diagnoses occurred among patients prescribed OxyContin after abuse-deterrent characteristics were introduced that did not occur with comparator opioids. Differentiation in abuse reductions between OxyContin and comparator opioids was the clearest among users of one opioid, since diagnoses could result from non-abuse-deterrent opioids among multiple-opioids users.

828. Bone Pain, Skeletal-Related Events and Opioid Analgesic Use in Prostate Cancer Patients with Bone Metastases

Adriana Valderrama,[2] Sara Eapen,[1] Kelly A. Hennessey,[1] Casey Jones,[1] Lonnie Wen,[2] Joseph Germino,[2] Mei S. Duh.[1] *[1]Analysis Group, Boston, MA, USA; [2]Bayer Healthcare, Whippany, NJ, USA.*

Background: Prostate cancer (PC) patients with bone metastases experience debilitating pain that is associated with increased morbidity and mortality. Opioid analgesics in conjunction with other treatments are indicated for the management of severe pain.

Objectives: Given the limited availability of real world data on its use, this study aims to estimate the prevalence of and predictors for opioid analgesic use in PC patients with bone metastases.

Methods: Electronic medical records (EMR) from US community oncology clinics captured in Altos Solutions' OncoEMR® database were used to identify PC patients with bone metastases. Opioid use was identified from EMR, while evidence of bone pain and skeletal-related events (SREs), including pathological fracture, surgery, radiotherapy to bone, and spinal cord compression were extracted from patients' medical charts. Prevalence of opioid use was evaluated for the overall sample and for the subset with bone pain. Predictors for opioid versus non-opioid analgesic use for pain were identified using a multivariate logistic model.

Results: In the study cohort of 1520 PC patients with bone metastases, the average age was 73.6 years and mean follow-up from bone metastases was 13.8 months. Of 927 PC patients with evidence of bone pain, 63% were opioid users, of whom 14% were chronic users. Multivariate regression analyses revealed that SREs significantly increased the opioid use risk by 3.21-fold (95%CI: 2.38–4.32), with the following additional significant risk factors: Medicare versus other/no insurance (OR = 1.54, 95%CI: 1.13, 2.10), chemotherapy (OR = 3.34, 95%CI: 2.17, 5.13), and NSAIDs use (OR = 1.90, 95%CI: 1.25, 2.88). Denosumab use was associated with a lower likelihood of opioid use (OR = 0.28, 95%CI: 0.17, 0.47).

Conclusions: SREs are a significant predictor for opioid analgesic use. Pain and symptom palliation is a significant management issue in PC. Appropriate treatments that delay or prevent SREs and effectively control pain are important in the management of these patients.

829. Evaluating the Effectiveness of the Soliris REMS Program

Alexander Cole,[1] Camille Bedrosian,[2] Arshadul Haque,[3] Arshad Mujeebuddin,[3] Amanda Wilson,[1] Jenifer Wogen,[1] John Price.[3] *[1]Epidemiology, Alexion Pharmaceuticals, Cheshire, CT, USA; [2]Research and Development, Alexion Pharmaceuticals, Cheshire, CT, USA; [3]Pharmacovigilance, Alexion Pharmaceuticals, Cheshire, CT, USA.*

Background: Soliris (eculizumab) is a complement inhibitor indicated for treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Soliris has had a boxed warning for serious meningococcal infections since approval. In 2010, a REMS was established to minimize the occurrence and morbidity associated with meningococcal infections.

Objectives: To determine the effectiveness of the Soliris REMS.

Methods: Post-marketing cases of meningococcal infection were identified from the Alexion Pharmacovigilance database. Person-years (PY) of eculizumab exposure by year were estimated from cumulative patients treated to 31 March 2014. Incidence rates of meningococcal infection since availability of eculizumab were calculated. Meningococcal vaccination was confirmed by each patient's healthcare provider, and vaccination rates were calculated as of 31 March 2014. Surveys to Health Care Professionals (HCPs) and patients were carried out to assess knowledge of REMS elements.

Results: In the USA, from 2007 through March 2014, there were 16 cases of meningococcal infection identified out of 5207 PY of eculizumab exposure (incidence rate of 0.31 per 100 PY). Comparable rates were observed outside of the USA (0.33 per 100 PY). Incidence during eculizumab clinical trials was 0.83 per 100 PY. Vaccinations were confirmed in 97% of patients; in 2.4% of patients, providers did not release patient information, and in 0.6%, a medical reason was given (e.g. co-existing acute condition and bone marrow transplant). Surveys indicated that 87% of patients stated their HCP offered to explain the Medication Guide, 99% knew what to do if there were signs or symptoms of infection and 96% carried the Patient Safety Card at all times. HCP surveys indicated that 99% identified the vaccine requirement correctly, and 88% stated that they reviewed the Medication Guide with their patients.

Conclusions: The Soliris REMS is effective in minimizing the occurrence and morbidity of meningococcal infection. Understanding of the risks associated with eculizumab treatment among HCPs and patients is high, resulting in nearly universal meningococcal vaccination among patients treated with eculizumab.

830. Association between Renin-Angiotensin System Inhibitors and Cancer Risk; Data Mining of a Spontaneous Reporting Database and a Claims Database

Mai Fujimoto,[1] Tomoya Higuchi,[1] Kouichi Hosomi,[1] Mitsutaka Takada.[1] [1]*Kinki University, Higashi-osaka, Osaka, Japan.*

Background: The interest has been focused on the potential risk of cancer associated with renin–angiotensin system inhibitors (angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARB]). However, it remains uncertain whether renin–angiotensin system inhibitors are associated with cancer.

Objectives: The aim of our study was to examine the association of renin–angiotensin system inhibitors and the risk of ten major cancers by employing different approaches.

Methods: The data from the first quarter of 2004 through 2012 were downloaded from the US Food and Drug Administration Adverse Event Reporting System (FAERS). A total of 54 841 322 drug-reaction pairs among 3 308 116 reports were analysed. The reporting odds ratio (ROR) and the information component (IC) were used to detect the risk signal. The lower limit of the 95% confidence interval (95%CI) of ROR 1 and IC 0 indicate risk signals. Furthermore, employing the claims database contains 1.2 million insured persons, the event sequence symmetry analysis (ESSA) was used to identify the risk of cancer after using renin–angiotensin system inhibitors over the period of January 2005 to July 2013. The lower limit of the 95%CI of adjusted sequence ratio (SR) >1 signified the risk of cancers. The Visual Mining Studio software (version 8.0) was used in the present study.

Results: The significant signals for bladder cancer were found for ACE inhibitors with (ROR; 1.23, 95%CI; 1.11–1.37, CI; 0.30, 95%CI; 0.14–0.45, ASR; 2.70, 95%CI; 1.38–5.68), and the significant signals for pancreatic cancer ware found for ARB with (ROR; 1.54, 95%CI; 1.38–1.73, CI; 0.61, 95%CI; 0.44–0.78, ASR; 1.35, 95%CI; 1.15–1.60).

Conclusions: Multi-methodological approaches suggest that renin–angiotensin system inhibitors are associated with an increased risk for bladder and pancreatic cancers. The risk of these cancers associated with renin–angiotensin system inhibitors is important and should be closely monitored in clinical practice.

831. Instructions for Clinical and Biomarker Monitoring in the Summary of Product Characteristics (SmPC) of Psychotropic Drugs: Overview and Applicability in Clinical Practice

Mariette Nederlof,[1,2] Lennart J. Stoker,[2,3] Toine C.G. Egberts,[1,4] Eibert R. Heerdink.[1] [1]*Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands;* [2]*Brocacef Ziekenhuisfarmacie,*

Maarssen, The Netherlands; [3]Saltro Diagnostic Centre, Utrecht, The Netherlands; [4]Clinical Pharmacy, University Medical Center, Utrecht, The Netherlands.

Background: The Summary of Product Characteristics (SmPC) of psychotropic drugs includes instructions for clinical and biomarker monitoring intended to optimize effectiveness and minimize harm.

Objectives: The present study evaluated which monitoring instructions are given in SmPCs, determined the reasons for these monitoring instructions and assessed whether these instructions were informative enough to be applicable in clinical practice.

Methods: Instructions for monitoring were collected from SmPCs of all psychotropic drugs available in the Netherlands ($n=73$). Reasons and requirements for monitoring were assessed. Monitoring of somatic markers was distinguished from non-somatic markers. The applicability was determined using the Systematic Information for Monitoring (SIM) score. Instructions were considered applicable when a SIM-score was ≥3.

Results: An average of 3.2 monitoring instructions per drug label was found with a large variability ranging from 0 to 13 instructions. Monitoring of suicidal thoughts and symptoms was most frequently mentioned in the SmPC. The main reason for monitoring was for safety (78%). Monitoring was predominantly mandatory (71%). Somatic parameters were most often mentioned (in 80% of the psychotropic drugs). Only 34% of the instructions were determined applicable in clinical practice.

Conclusions: Prescribing of psychotropic drugs is accompanied by diverse monitoring instructions aimed at improving safe use. However, two-thirds of the instructions on monitoring do not provide sufficient information to be applicable in clinical practice.

832. Assessment of Metabolic Monitoring by Physicians of Patients Treated with Quetiapine in Selected European Countries

Robert S. Brody,[1] Charlie L. Liss,[1] Heather Wray,[2] Ramon Iovin,[3] Carmen Michaylira,[4] Catherine Datto,[5] Leigh Jefferies,[5] Anneli Thuresson.[2] *[1]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA; [2]AstraZeneca R&D, Mölndal, Sweden; [3]Formerly Adelphi Values, Boston, MA, USA; [4]Adelphi Research, Doylestown, PA, USA; [5]AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA.*

Background: A physician survey was used to evaluate the effectiveness of risk minimization of physician educational materials following distribution in eight EU countries. Content was agreed to with the respective national authorities.

Objectives: To assess physicians' metabolic monitoring of patients (pts) treated with quetiapine IR and quetiapine XR and to assess recall of the receipt of previously distributed educational materials. The evaluation was to include both process and outcome measures in accordance with new EMA pharmacovigilance guidance.

Methods: Randomly selected physicians from each of eight EU countries were invited to complete an Internet-based survey. Survey questions included performance of specific metabolic monitoring activities, awareness that pts were monitored within or outside of their practice and recall of receiving the materials. Results were reported using descriptive statistics and 95% confidence intervals. Monitoring was compared against acceptable levels (which varied according to monitoring activity and fixed at a level of 70-80%) defined by scientific advisors and local company personnel with knowledge of professional guidelines and health care delivery within each country.

Results: Eight hundred surveys (100 per country) were included in the final analysis. A high level of awareness (proxy measure of process) was seen, with physicians reporting that 64.5% of pts receiving quetiapine were monitored within their practice or by others. Thirty-seven percent of physicians recalled receiving the materials, of whom 90.6% reported reading these, whereas 35% were uncertain of having received the materials. Outcome measures (defined by reported monitoring behaviours) were generally higher (>10%) among physicians who reported receiving the educational materials than those who did not.

Conclusions: This study demonstrated that self-reported metabolic monitoring of pts treated with quetiapine were at acceptable levels on the basis of locally defined and at a fixed-level of acceptability (based upon UK where performance is incentivized). Receipt of materials may have accounted for higher levels of monitoring.

833. Objective Assessment of Metabolic Monitoring in Patients Treated with Seroquel IR/XR in the UK and Germany Using Electronic Medical Records (EMR)

Robert S Brody,[1] Charlie L. Liss,[1] Heather Wray,[2] Anushini Muthutantri,[3] Catherine Datto,[4] Leigh Jefferies.[4] *[1]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA; [2]AstraZeneca R&D, Mölndal, Sweden; [3]IMS Health, London, UK; [4]AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA.*

Background: A PASS to evaluate the effectiveness of risk minimization via physician educational materials on metabolic monitoring for patients (pts) prescribed Seroquel IR/XR, quetiapine (QTP) was proposed as an objective assessment of the medical monitoring performed. Physician specialties targeted to receive the educational materials in each country were selected in agreement with respective national regulatory authorities.

Objectives: To provide an objective assessment of metabolic monitoring of pts by UK GP's and German specialists prescribing QTP following the distribution of educational materials.

Methods: A retrospective study of metabolic monitoring outcomes among pts treated with QTP during a 7-month study period from the IMS Disease Analyzer electronic medical records (EMR) database included: recording of weight at start, and during, quetiapine treatment; monitoring of lipids; signs and symptoms (S/S) of hyperglycemia; blood glucose in those with, or at risk for diabetes mellitus; lifestyle counseling. Data reported in EMR text fields were not evaluated. Results were reported using descriptive statistics and 95% confidence intervals.

Results: In the UK, 16–67% of GP practices monitored >50% of pts treated. The highest and lowest prevalence of monitoring by UK GPs were for, respectively, S/S of hyperglycemia in pts with diabetes (50.6% of eligible pts) and assessment of lipids (27.7% of eligible pts). Other monitoring by UK GPs was performed in 31–39% of eligible pts. Higher levels of monitoring by GPs were found for each monitoring activity in the 12 months prior to the study period, when monitoring was performed in 45–81% of eligible pts. Metabolic monitoring was rarely documented among specialists in Germany (<2% of specialist practices monitored >50% of pts).

Conclusions: These findings may be explained by "shared care" arrangements and the organization of healthcare services within communities, i.e., specialists may expect/assume the monitoring is performed by GPs. The study findings may also be limited since data entered as free text in EMR were not considered in the evaluation.

834. Risk Minimization and Assessment of Olanzapine Long-Acting Injection in 21 Countries in Europe

Meghan E. Jones,[1] Holland C. Detke,[1] Rashna Chhabra-Khanna.[2] *[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Eli Lilly and Company, Surrey, UK.*

Background: The ZypAdhera Healthcare Awareness Programme (HAP) is a training for olanzapine long-acting injection (OLAI) for healthcare professionals (HCPs) on the safe use of the product. An assessment of this training, the Post-Injection Syndrome Survey, was conducted in 21 European countries 6 to 12 months post-launch among HCPs who received this training.

Objectives: To evaluate HCPs' awareness and understanding of the importance of adherence to the OLAI label.

Methods: A web-based survey was conducted in four waves from 2009–2012 based on OLAI launch timing in 21 countries in Europe. The survey was designed to assess understanding of three key risk messages (KRMs): (1) awareness of the risk of post-injection syndrome, (2) conditions of safe use, and (3) reconstitution of OLAI. Survey invitations were sent to all HCPs who received HAP training in each country. The data were analyzed using descriptive statistics, and percent of correct responses were calculated with 95% confidence intervals (CI) for each KRM. Data were stratified by prescriber status.

Results: A total of 5.8% ($N = 817$) of the 13 992 invited HCPs completed the survey. The survey completion rate ranged from 2.2% to 24.2% across countries. Thirty-four percent of the HCPs identified themselves as OLAI prescribers. The proportion of responders who answered correctly for the KRMs was 82.0% (95%CI: 79.2–84.6) for KRM 1, 68.8% (95%CI: 65.5–72.0) for KRM 2 and 69.6% (95%CI: 66.4–72.8) for KRM 3. The results among the prescribers were similar to all responders with KRM 1 being slightly lower at 74.8% (95%CI: 69.3–79.8), KRM 2 was 70.5% (95%CI: 64.8–75.8) and KRM 3 was higher at 80.6% (95%CI: 75.4–85.1).

Conclusions: The results from the four survey waves have been similar and consistent, indicating continued effectiveness of the HAP. Results of the survey suggest that HCPs that received the HAP across diverse countries and healthcare practices in Europe understand the most important aspects of the OLAI label and KRMs, and the potential risk of post-injection syndrome appears to be well-recognized.

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835. National Trends in Treatment with Prescription Medications With Risk Evaluation and Mitigation Strategies in the United States, 2003–2010

Rachel Harrington,[1] Dima M. Qato.[1] [1]*Dept. of Pharmacy Systems, Outcomes and Policy, University of Illinois at Chicago, Chicago, IL, USA.*

Background: While prescription medications with risk evaluation and mitigation strategies are defined as potentially high risk, little is known about their utilization in the outpatient, office-based, setting.

Objectives: To examine nationally representative estimates of the prevalence and patterns in treatment for prescription medications with risk evaluation and mitigation strategies (REMS) and to characterize the patient and provider characteristics associated with their utilization.

Methods: A sample of visits from the 2003 to 2010 National Ambulatory Medical Care Survey (NAMCS), a survey of outpatient, office-based visits, was weighted to produce national estimates. The key outcome was prevalence of prescription treatment visits with a REMS prescription.

Results: A quarter of treatment visits between 2003 and 2010 included prescription of at least one REMS drug (25.5%, 95% confidence interval [CI] 24.8–26.1%), ranging from 19.8% (CI: 18.5–21.2%) in 2003 to 27.3% (CI: 25.5–29.1%) in 2010. There was a 5% annual increase in the odds of a REMS prescription (odds ratio [OR] 1.05, CI 1.04–1.07) and a 9% annual increase in the odds of receiving more than one REMS drug per visit (OR: 1.09, CI: 1.06–1.11). This trend was consistent across REMS therapeutic classes, with four of the top five showing similar, statistically significant, increases in the within-class odds of REMS prescription. In multivariate analysis, patients aged 65 years and older had significantly higher odds of REMS prescription than those 25 to 45 years of age (OR: 1.35, CI: 1.24, 1.48). Payment with public (versus private) insurance was also significantly associated with the outcome (Medicare OR: 1.29, CI: 1.20, 1.39; Medicaid OR: 1.24, CI: 1.14, 1.34). The adjusted yearly trend was consistent with the unadjusted trend (OR: 1.04, CI: 1.03, 1.06).

Conclusions: In a nationally representative sample of US outpatient office visits, high-risk medications were prescribed in more than one-quarter of treatment visits, with increasing prevalence over time, independent of overall prescribing trends. Older patients and patients with public insurance are particularly at-risk.

836. Trends in the Safety of New Molecular Entities and Therapeutic Biologics Approved by the FDA (1980–2014)

Enrique Seoane-Vazquez,[1] Rosa Rodriguez-Monguio.[2] [1]*International Center for Pharmaceutical Economics and Policy, Massachusetts College of Pharmacy and Health Sciences, Boston, MA, USA;* [2]*Health Policy and Management, School of Public Health, University of Massachusetts Amherst, Amherst, MA, USA.*

Background: The FDA assesses information submitted by sponsors, the nature of the disease, the risk / benefit of available therapies, and the feasibility of risk management tools to determine whether the benefits of a new drug outweigh its risks. The FDA may require from a drug sponsor to add a boxed warning to the label, create a patient medication guide, or implement a Risk Evaluation and Mitigation Strategy (REMS) anytime during the life of the drug. The FDA can withdraw from the market any product that is not safe under its conditions of use.

Objectives: To assess trends in the safety of new molecular entities (NME) and therapeutic biologics (BLA) approved by the FDA in the period 1980–2014.

Methods: Information about approvals and safety regulatory actions was extracted from the FDA webpage and Physician Reference Books 1980–2014. Data were updated to 31 December 2014. Descriptive analysis and chi-square tests were conducted in the analysis.

Results: The FDA approved 970 drugs (89.3% NME, 10.7% BLA) in the period 1980–2014. There were 225 approvals in the 1980s, 339 in the 1990, 251 in the 2000s, and 155 in 2010-2014. There were 210 orphan drug product (23.3% of 903 drugs approved after implementation of the Orphan Drug Act). The percentage of products with a black boxed warnings (1980s=28.9%, 1990s=32.2%, 2000s=36.3%, 2010-2014=39.4%), medication guides (9.8%,13.9%,25.5%,32.3%, respectively), and REMS (3.8%,1.5%, 9.2%,16.8%, respectively) significantly increased over time. The percentage of safety withdrawals was 4.4%,5.0%,2.0% and 0.6%, respectively. Musculo-skeletal system (85.4% of drugs having at

least one FDA safety regulatory action) was the therapeutic class with the largest percentage of drugs with FDA safety actions, and sensory organs (0.0%) was the therapeutic class with the lowest percentage. Safety data are right censored, and changes in FDA safety regulatory actions are expected over time.

Conclusions: The percentage of products with safety problems increased over time. This increase maybe be explained in by changes in FDA criteria for assessing the risk/benefit of drugs and by changes in the orphan status and therapeutic classes of approved products.

837. Assessing Cost-Effectiveness of HPV Vaccines with Decision Analytic Models: What Are the Distinct Challenges of Low And Middle Income Countries? A Protocol for a Systematic Review

Obinna I. Ekwunife,[1,2] Andreas Gerber Grote,[3] Christoph Mosch,[4] James F. O'Mahony,[5] Stefan K. Lhachimi.[1] *[1]Cooperative Research Group for Evidence-based Public Health, Department of Prevention and Evaluation, Leibniz Institute for Prevention Research and Epidemiology – BIPS Bremen, Bremen, Germany; [2]Department of Clinical Pharmacy and Pharmacy Management, Nnamdi Azikiwe University, Awka, Anambra, Nigeria; [3]Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany; [4]Institute for Research in Operative Medicine (IFOM), Universität Witten/Herdecke, Witten, Germany; [5]Department of Health Policy and Management, School of Medicine, Trinity College Dublin, Dublin, Ireland; [6]Institute for Public Health and Nursing Research – IPP, Health Sciences Bremen, University of Bremen, Bremen, Germany.*

Background: Cervical cancer poses a huge health burden, both to developed and developing nations, making prevention and control strategies necessary. However, the challenges of designing and implementing prevention strategies differ for low-income and middle-income countries (LMICs) as compared to countries with fully developed healthcare systems. Moreover, for many LMICs, much of the data needed for decision analytic modelling, such as prevalence, will most likely only be partly available or measured with much larger uncertainty. Lastly, imperfect implementation of human papillomavirus (HPV) vaccination may influence the effectiveness of cervical cancer prevention in unpredictable ways. This systematic review aims to assess how decision analytic modelling studies of HPV cost-effectiveness in LMICs accounted for the particular challenges faced in such countries.

Objectives: This protocol describes a systematic review that aims to review cost-effectiveness studies of HPV vaccination for LMIC with a view of how decision analytic modelling studies accounted for the distinctive challenges of LMIC.

Methods: We will conduct a systematic review to identify suitable studies from MEDLINE (via PubMed), EMBASE, NHS Economic Evaluation Database (NHS EED), EconLit, Web of Science, and CEA Registry. Searches will be conducted for studies of interest published since 2006. The searches will be supplemented by hand searching of the most relevant papers found in the search. Studies will be critically appraised using Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist. We will undertake a descriptive, narrative, and interpretative synthesis of data to address the study objectives.

Results: The review will ascertain: (1) whether the existing literature on cost-effectiveness modelling of HPV vaccines acknowledges the distinct challenges of LMICs, (2) how these challenges were accommodated in the models, (3) whether certain parameters systemically exhibited large degrees of uncertainty due to lack of data and how influential were these parameters on model-based recommendations, and (4) whether the choice of modelling herd immunity influences model-based recommendations, especially when coverage of an HPV vaccination program is not optimal.

Conclusions: The proposed systematic review will assess how the cost-effectiveness studies of HPV vaccines accounted for the distinct challenges of LMICs. The gaps identified will expose areas for additional research as well as challenges that need to be accounted for in future modelling studies. Systematic review registration PROSPERO CRD42015017870. http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015017870#.VVBuI44irIU.

838. Costs, Resource Utilization, and Treatment Patterns for Patients with Metastatic Melanoma

Edmond L. Toy,[1] Michael C. Lewis,[1] Alan K. Oglesby,[2] Mei S. Duh,[3] Francis Vekeman.[4] *[1]Analysis Group, Inc., Denver, CO, USA; [2]US Health Outcomes,*

GlaxoSmithKline, Research Triangle Park, NC, USA; [3]Analysis Group, Inc., Boston, MA, USA; [4]Groupe d'analyse, Ltee, Montreal, QC, Canada.

Background: Metastatic melanoma (MM) is an aggressive cancer that is difficult to treat. This is one of the first studies to examine the real-world costs and treatment patterns in patients with MM since the approval of ipilimumab and vemurafenib in the USA in 2011.

Objectives: To estimate the real-world healthcare costs and resource utilization (RU) among MM patients in the USA who were administered at least one therapy recommended in current treatment guidelines.

Methods: Administrative claims data from the Truven MarketScan database (2010–2012) were used. MM patients, identified using ICD-9 codes, were stratified by their first use of a recommended systemic therapy: ipilimumab, vemurafenib, interleukin-2 (IL-2), dacarbazine, temozolomide, or paclitaxel. Follow-up began with initiation of therapy to the end of insurance eligibility or data availability. Primary outcomes were all-cause healthcare costs (2013 US dollars) and RU per patient per month (PPPM). Regression models adjusting for baseline characteristics were used to assess cost and RU differences between ipilimumab and vemurafenib patients.

Results: A total of 834 MM patients were included. The most common initial therapies were ipilimumab (32%) and vemurafenib (28%). Ipilimumab patients were older than vemurafenib patients (62.3 vs 58.4 years, $p < 0.001$). Costs were highest for the ipilimumab and IL-2 cohorts (~$35,000 PPPM) and were >2× higher than other cohorts. Adjusted total costs were $18,337 PPPM higher for ipilimumab vs. vemurafenib cohorts ($p < 0.001$). Compared to vemurafenib patients, ipilimumab patients had no statistically significant differences in the rate of hospitalizations (adjusted incidence rate ratio [aIRR]: 0.90, $p = 0.455$) and ER visits (aIRR: 0.78, $p = 0.172$) but had fewer outpatient visits excluding treatment visits (aIRR: 0.81, $p < 0.001$). Ipilimumab and vemurafenib patients received a second therapy less frequently than IL-2 and dacarbazine patients.

Conclusions: Ipilimumab and vemurafenib were quickly adopted and were the most frequently used therapies for MM by 2012. The cost and RU burden for MM is high and varies substantially across treatment cohorts.

839. Clinical and Economic Benefits of Extended Treatment with Apixaban for the Treatment and Prevention of Recurrent Venous Thromboembolism in Canada

Peter Quon,[1] Hoa H. Le,[2] Vincent Raymond,[3] Mondher Mtibaa,[4] Andriy Moshyk.[4] *[1]Evidera, Inc., Bethesda, MD, USA; [2]Evidera, Inc., Lexington, MA, USA; [3]Pfizer Canada, Inc., Kirkland, QC, Canada; [4]Bristol-Myers Squibb Canada, Montreal, QC, Canada.*

Background: Venous thromboembolism (VTE) is associated with long-term clinical and economic burden. Clinical guidelines recommend at least 3 months of anticoagulation for most VTE patients, but concerns over bleeding risk often limit extended treatment in clinical practice. Apixaban has been studied for extended VTE treatment in the AMPLIFY-EXT trial, demonstrating superiority to placebo in VTE reduction without increasing risk of major bleeding.

Objectives: This study assessed the long-term clinical and economical benefits of extending apixaban an additional 12 months beyond an initial 6 months when clinical equipoise exists compared to 6 months of standard of care (SoC; enoxaparin/warfarin) in the treatment and prevention of recurrent VTE in Canada. Apixaban was also compared to other novel oral anticoagulants (NOACs; rivaroxaban and dabigatran) for extended treatment. Other durations of therapy were assessed in scenario analyses.

Methods: A Markov model was developed to simulate patients with VTE over their lifetime. Patients were at risk of VTE, bleeding, and death. Efficacy and safety for apixaban and SoC were based on data from AMPLIFY and AMPLIFY-EXT, while estimates of relative efficacy to other NOACs were based on a network meta-analysis. Patient quality-adjusted life years (QALYs) were based on published utilities with a preference for Canadian-based studies. Costs for healthcare resource utilization were from a Ministry of Health perspective and expressed as 2014 CAD ($).

Results: Extended treatment with apixaban compared to SoC resulted in fewer recurrent VTE, VTE-related deaths, and bleeding events but at slightly increased cost, resulting in an incremental cost-effectiveness ratio (ICER) of $4828 per QALY gained. Compared to other NOACs, apixaban had the superior bleeding profile and was the dominating (more effective and less costly) strategy. In sensitivity analyses on other treatment durations, apixaban was still cost-effective against all strategies.

Conclusions: Extended treatment with apixaban can offer substantial clinical benefits and is a cost-effective alternative to SoC and other NOACs.

840. The QUA-VKA Study to Identify New Risk Factors for Bleeding During Treatment with Vitamin K Antagonists: Objectives and Design

Nienke van Rein,[1,2] Mettine H.A. Bos,[1,2] Willem M. Lijfering,[1,2,3] Felix J.M. van der Meer,[1] Pieter H. Reitsma.[1,2] *[1]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands; [2]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands; [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.*

Background: Patients who use vitamin K antagonists (VKA) are at increased risk of bleeding. Reported prediction scores for major bleeds perform modestly, necessitating the need for new predictors in this patient group.

Objectives: The QUA-VKA prospective cohort study aims to identify new risk factors that contribute to the prediction of bleedings in patients who start VKA treatment. Here, we delineate the objectives of the study, principal methodological features, and timeline.

Methods: All patients starting VKA treatment at three Dutch anticoagulation clinics between 1 January 2012 and 1 July 2014 were included according to an opt-out procedure that was approved by the local medical ethical committee. Leftover plasma following analysis of the international normalized ratio was stored, and patients were followed until a major bleed, end of VKA treatment, death, or the end of the study (31 December 2014), whichever occurred first.

Results: Of 16 278 consecutive patients who started VKA treatment, 136 (1%) patients opted out, leaving 16,142 included patients. We obtained plasma from 13 528 patients (84%) as logistic complications prevented plasma collection for 2614 (16%) patients. 8545 Patients were male (52%), with a mean age of 70 years (SD 14) and the INR target range was 2.5–3.5 in 14,807 patients (91%). Preliminary results from two anticoagulation clinics showed that 306 major bleeds occurred during 15,188 years of follow-up (incidence rate 2.02/100 person years, 95%CI 1.80–2.25), of which 121 (incidence rate 3.84/100 person years, 95%CI 3.20–4.57) and 156 (incidence rate 2.66/100 person years, 95%CI 2.26–3.10) occurred during the first 3 and 6 months of VKA treatment, respectively.

Conclusions: Long-term biological sample storage will allow for the investigation of biomarkers that may predict bleeding and other diseases. The coagulation factors VIII and von Willebrand factor are currently analyzed, and their association with major bleeds during VKA treatment will be available at the time of the ICPE2015.

841. Rivaroxaban versus Warfarin: Effect on Healthcare Resource Utilization and Costs in Nonvalvular Atrial Fibrillation Patients

François Laliberté,[1] Concetta Crivera,[2] Winnie W Nelson,[2] William H Olson,[2] Jeffrey Schein,[2] Guillaume Germain,[1] Patrick Lefebvre.[1] *[1]Groupe d'Analyse, Ltée, Montréal, QC, Canada; [2]Janssen Scientific Affairs, Raritan, NJ, USA.*

Objectives: To assess the effect of rivaroxaban vs. warfarin on healthcare resource utilization and costs in propensity matched rivaroxaban and warfarin users with NVAF.

Methods: Healthcare claims from the Humana database from 5/2011 to 12/2012 were analyzed. Adult patients newly initiated on rivaroxaban or warfarin, with ≥2 AF diagnoses (ICD-9-CM: 427.31), and without valvular AF were identified. Based on propensity score methods, warfarin patients were matched 1:1 to rivaroxaban patients. Patients were observed up to end of data availability, end of insurance coverage, death, a switch to another anticoagulant, or treatment non-persistence. The total number of hospitalization days, resource utilization (hospitalizations, outpatient visits, and ER visits), and corresponding costs including pharmacy costs were evaluated using Lin's method.

Results: Matches were found for all rivaroxaban patients and characteristics of the matched groups ($n = 2253$ per group) were well balanced. The all-cause mean total numbers of hospitalization days and outpatient visits were significantly lower for rivaroxaban compared to warfarin (2.71 vs. 3.87 days, $p = 0.032$; 25.3 vs. 35.8 days, $p < 0.001$), while the difference for mean number of ER visits was not significant. Mean all-cause and AF-related hospitalization costs were significantly lower for rivaroxaban vs. warfarin

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patients (all-cause: $5411 vs. $7427, $p=0.047$; AF-related: $2872 vs. $4147, $p=0.020$). Including anticoagulant costs, mean overall total all-cause costs were comparable for rivaroxaban vs. warfarin users due to cost offset from a reduction in the mean numbers of days hospitalized and outpatient visits, but not statistically different (all-cause: $17,590 vs. $18,676, $p=0.542$; AF-related: $7394 vs. $7319, $p=0.943$).

Conclusions: Despite higher rivaroxaban anticoagulant costs, mean overall total all-cause and AF-related costs remain comparable for patients with NVAF treated with rivaroxaban versus warfarin due to cost offset from lower mean numbers of hospitalization days and outpatient visits.

842. Health Utilities Associated With Bleeding Control and Adverse Events in Premenopausal Women with Uterine Fibroids

Seung-Mi Lee,[1] Insun Choi,[1] Soyun Kim,[1] Sung-Jin Park,[1] Dong-churl Suh.[1] *[1]College of Pharmacy, Chung-Ang University, Seoul, Korea.*

Background: Most existing hormonal treatments for uterine fibroids accompanied by heavy menstrual bleeding have frequently reported with menopause-like symptoms as adverse events, while new oral drugs such as selective progesterone-receptor modulators control uterine bleeding effectively and are less likely to cause menopause-like symptoms.

Objectives: To elicit utility values for health states associated with bleeding control and adverse events of preoperative medication therapy in premenopausal women with uterine fibroids in South Korea.

Methods: Health state 'vignettes' related to preoperative medication therapy for uterine fibroids were developed for: (i) heavy menstrual bleeding, (ii) bleeding control without menopause-like symptoms, (iii) bleeding control with mild menopause-like symptoms, (iv) bleeding control with moderate menopause-like symptoms, and (v) bleeding control with severe menopause-like symptoms. Descriptions for health states were developed based on published literature and consultations with clinical specialists. Using the standard gamble method, vignettes were valued by interviewing Korean women aged 20–49 years. The statistical influence of decrement in health utilities due to menopause-like symptoms was tested using paired *t*-tests.

Results: Ninety one Korean women were interviewed. They were 34.8 (±9.1) years old. Mean utilities were 0.58 (±0.21) for heavy menstrual bleeding, 0.83 (±0.19) for bleeding control without menopause-like symptoms, 0.70 (±0.23) for bleeding control with mild menopause-like symptoms, 0.59 (±0.19) for bleeding control with moderate menopause-like symptoms, and 0.43 (±0.20) for bleeding control with severe menopause-like symptoms. The decremented utilities were 0.13 (95%CI: 0.10–0.16) for mild menopause-like symptoms, 0.24 (0.21–0.27) for moderate menopause-like symptoms, 0.40 (0.36–0.43) for severe menopause-like symptoms compared to bleeding control without menopause-like symptoms.

Conclusions: This study found that bleeding and/or adverse events of menopause-like symptoms significantly reduced health-related quality of life for premenopausal women with uterine fibroids.

843. A Cost-Effectiveness Analysis of Opioid Substitution Therapy upon Release in Reducing Mortality among Prisoners with a History of Opioid Dependence

Natasa Gisev,[1] Marian Shanahan,[1] Don J. Weatherburn,[2] Richard P. Mattick,[1] Sarah Larney,[1,3] Lucy Burns,[1] Louisa Degenhardt.[1,4] *[1]National Drug and Alcohol Research Centre, UNSW Australia, Sydney, NSW, Australia; [2]New South Wales Bureau of Crime Statistics and Research (BOCSAR), Sydney, NSW, Australia; [3]Alpert Medical School, Brown University, Providence, RI, USA; [4]School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia.*

Background: Although opioid substitution therapy (OST) in the immediate period after prison release has been shown to reduce mortality, the cost-effectiveness has not yet been examined.

Objectives: To undertake a cost-effectiveness analysis of the immediate treatment with OST at the time of prison release and prevention of death in the first 6 months post-release.

Methods: Population-based, retrospective data linkage study using records of all OST entrants in New South Wales, Australia (1985–2010), court appearances (1993–2011) and prison episodes (2000–2012). The cohort included 16,073 people who were released from prison for the first time between 1 January 2000

and 30 June 2011. At the point of prison release, 7892 people received OST treatment and 8181 did not receive OST treatment. Propensity scores were used to match individuals in the two groups, and mortality and the total costs (treatment, prison, court, penalties and crime) incurred in each group were evaluated at 6 months post-release.

Results: During the 6-month observation period, 23 (0.3%) people who were released onto OST died, compared to 58 people (0.7%) who were not released onto OST ($p = 0.001$). The incremental cost-effectiveness ratio was −$714, indicating that the group which did not receive OST upon release incurred both higher costs and there were more deaths. Furthermore, the probability that OST post-release is cost-effective per life-year saved is 99.98% at a willingness to pay of $500.

Conclusions: Compared to no treatment on release, OST is cost-effective in reducing mortality among prisoners with a history of opioid dependence in the first six months of prison release.

844. A Cost Comparison of Split-Dose Reduced-Volume Oral Sulfate Solution (OSS) and Polyethylene Glycol with Electrolytes Solution (PEG-ELS)

Mark Cleveland,[3] Sander Yermakov,[1] Matthew Davis,[1] Romaine Campbell,[1] Lynn Huynh,[1] Francis A. Farraye,[2] Mihran Yenikomshian.[1] *[1]Analysis Group, Inc., Boston, MA, USA; [2]Boston Medical Center, Boston, MA, USA; [3]Braintree Labtoratories, Inc., Braintree, MA, USA.*

Background: Colorectal cancer is a costly disease, with costs increasing dramatically based on disease progression.

Objectives: The study aimed to (1) develop a cost model for colonoscopy preparation among patients referred for colonoscopy using split-dose reduced-volume oral sulfate solution (OSS) and generic polyethylene glycol with electrolytes solution (PEG-ELS), (2) examine cost-savings associated with OSS versus PEG-ELS, and (3) assess the robustness of the cost model.

Methods: Clinical efficacy of each agent was based on the results of a 541-patient clinical trial comparing OSS to PEG-ELS. Cleansing agent and colonoscopy procedure costs were calculated from OptumHealth Reporting & Insights claims data for 2010–Q1 2013. In the cost model, patients' colonoscopies were tracked until the patient reached age 75. The difference per patient per year (PPPY) in total cleansing agent and colonoscopy procedure costs over the time horizon between the OSS and PEG-ELS cohort was calculated. One-way sensitivity analyses were also conducted to test the robustness of the cost model.

Results: The cost model showed that OSS patients had fewer colonoscopies over the time horizon (OSS: 0.158 vs. PEG-ELS: 0.170 PPPY). Total PPPY costs were $280.34 for the OSS cohort and $296.36 for the PEG-ELS cohort, resulting in a cost-saving of $16.01 to the payer for the OSS cohort. Varying the annual colonoscopy completion rate, surveillance intervals, time horizon, and proportion of high-risk patients did not change the observation of cost-savings under OSS. Cost-savings switched from the OSS to the PEG-ELS cohort in three cases: (1) base-case cost of a completed colonoscopy decreased by 75%, (2) base-case cost of OSS increased to over $143 per usage, and (3) all non-completers were lost to follow up.

Conclusions: From a payer's perspective, the cost model showed that the use of OSS as the cleansing agent resulted in potential cost-savings compared with PEG-ELS. The cost model was robust and cost-savings under OSS remained in various sensitivity analyses.

845. Impact of Intensive and Maintenance Treatment of Pulmonary Tuberculosis on Respiration-Quality of Life in Indonesia

J. Atthobari,[1] H. Firmansyah,[2] U.A. Mulyani,[3] D. Perwitasari.[2] *[1]Faculty of Medicine, Universitas Gadjah Mada (UGM), Yogyakarta, Indonesia; [2]Faculty of Pharmacy, Universitas Ahmad Dahlan (UAD), Yogyakarta, Indonesia; [3]Clinical Epidemiology Unit, Ministry of Health, Republic of Indonesia, Jakarta, Indonesia.*

Background: Pulmonary tuberculosis (PTB) remains the most frequent, transmittable, life threatening and important infectious disease in Indonesia. The program for controlling and eliminations had been addressed using the multidrugs during intensive and maintenance treatment. Moreover, PTB resulted in anatomic and functional changes associated with pulmonary impairment that occurs frequently and varies in severity which could impact the quality of life (QoL).

Objectives: To determine QoL of PTB patients and to evaluate whether 2-month intensive and 4-month maintenance treatment affects the QoL.

Methods: A cross-sectional design was used for this study in adult, new cases of PTB in Lung Hospital and Primary Health Centers in Yogyakarta, Indonesia. A survey was performed by face-to-face interview. The translated and validated St. George Questionnaire (SGRQ) was used to assess respiration-QoL which contained 51 questions for dimensions of symptoms, activities, and disease impact. The measurement was done prior of the TB treatment and after intensive and maintenance phases of treatment using fixed dosed combination regimens.

Results: In total, 86 PTB patients were enrolled, aged 39.2 ± 14.4 years, and 60.5% were male. Total mean of SGRQ score for symptoms, activity and impacts were 49.5 ± 14.4; 43.5 ± 28.5; 39.8 ± 19.8, respectively. Lower impacts scores were found comparing with symptoms and activity ones. All scores were significantly ($p < 0.001$) lower after intensive therapy (23.9 ± 19.3; 27.3 ± 23.4; 21.0 ± 20.3, respectively) and after maintenance therapy (12.7 ± 14.9; 19.9 ± 20.2; 11.5 ± 17.3, respectively), indicating patient's symptoms, activities, and impact were significantly better compared to before treatment. The QoL was increased significantly ($p < 0.001$ adjusted by age and sex) from 0.70 ± 0.22 before treatment to 0.86 ± 0.13 and 0.91 ± 0.12 after intensive and maintenance therapy, respectively.

Conclusions: Patients with PTB were found relatively moderate respiration-related quality of life. Two months intensive and continued for 4 months maintenance treatment of pulmonary tuberculosis improve health-related quality of life

846. Cost Effectiveness of Melanoma Therapies

Karissa M. Johnston,[1] Emily McPherson,[2] Katherine Osenenko,[1] Joanna Vergidis,[2] Adrian Levy.[3] *[1]ICON Epidemiology, Vancouver, BC, Canada; [2]BC Cancer Agency, Vancouver/Victoria, BC, Canada; [3]Dalousie University, Halifax, NS, Canada.*

Background: Melanoma presents an important burden worldwide. Until recently, the prognosis for unresectable and metastatic melanoma was poor, with approximately 10% of metastatic melanoma patients surviving at 2 years. Introduction of newer therapies including ipilimumab, vemurafenib, dabrafenib, and trametinib has improved progression-free survival, with additional benefits anticipated from the forthcoming class of PD-1 inhibitors. Cost of therapy and resulting cost effectiveness are important factors in determining patient access to specific treatments.

Objectives: To review the published evidence regarding cost effectiveness of melanoma therapies, and provide an overview of the relative cost effectiveness of available therapies by disease stage.

Methods: A systematic literature review was undertaken to identify published articles of the cost effectiveness of available therapies for melanoma, using the keywords "melanoma" and "cost effectiveness" or "pharmacoeconomic." All published articles and abstracts describing the cost effectiveness of a therapeutic intervention for melanoma were eligible for inclusion.

Results: The initial literature search identified 174 titles; after abstract review of all titles and abstracts for relevance to inclusion criteria, and addition of articles identified through review of citations in included articles and review of conference abstracts and grey literature, a total of 15 articles were included in the review. Relative to standard of care chemotherapy, incremental cost effectiveness ratios for newer therapies ranged from $74K to $139K USD, higher than standard thresholds for establishing cost effectiveness.

Conclusions: Recent advances in the therapeutic options for advanced melanoma have brought about notable improvements in overall and progression-free survival. Given the acquisition costs associated with such therapies, economic analysis to identify the most cost effective therapies within key patient subgroups will be critical in ensuring that patients have access to effective therapies within the constraints of fixed healthcare budgets. A key requirement will be to assess the relative effectiveness of all available therapies, through head-to-head trials or indirect quantitative methods.

847. Predictors of High Healthcare Resource Utilization and Liver Disease Progression among Patients with Chronic Hepatitis C

Joyce LaMori,[1] Neeta Tandon,[1] François Laliberté,[2] Guillaume Germain,[2] Dominic Pilon,[2] Patrick Lefebvre,[2] Avinash Prabhakar.[1] *[1]Janssen Scientific Affairs, LLC, Titusville; [2]Groupe d'Analyse, Ltée, Montréal, QC, Canada.*

Background: Although the high cost burden of chronic hepatitis C (CHC) has been described in the literature, there is a lack of data on the assessment of characteristics associated with high healthcare utilizers.

Objectives: The purpose of this study was to identify demographics and clinical characteristics associated with high healthcare utilizers and liver disease progression among CHC patients.

Methods: Health insurance claims from 60 self-insured US companies were analyzed (01/2001–03/2013). Adult patients with ≥2 CHC claims (ICD-9-CM: 070.44 or 070.54), ≥6 months of continuous insurance coverage before the first CHC diagnosis and ≥36 months after were included. Patients with HIV were excluded. Demographics and baseline comorbidities including CHC-related and non-CHC-related conditions were described. Generalized estimating equations with logit link for binary outcomes were used to identify the most predictive demographics and clinical characteristics of being in the 20% of patients with the highest healthcare resource utilization (HRU). Predictive factors of liver disease progression were also identified.

Results: The mean age of the study population ($N = 4898$) was 52.4 years and 39.4% were female. Compensated cirrhosis, ESLD and both CHC-related and non CHC-related comorbidities were strong predictors of high healthcare costs, with odds ratios (ORs; 95%CI) for ESLD, ≥2 CHC-related, and ≥2 non CHC-related comorbidities of 3.31 (2.80–3.92), 2.78 (2.47–3.12), and 2.18 (1.75–2.71), respectively. CHC-related and non CHC-related comorbidities were also strong predictors of liver disease progression with ORs (95% CI) for ≥2 CHC-related and ≥2 non CHC-related comorbidities of 2.18 (1.83–2.60) and 1.50 (1.14–1.97), respectively.

Conclusions: This real-world study suggests that CHC patients with the highest HRU and costs had a high level of comorbidity at baseline and that non-CHC conditions are strong predictors of high healthcare costs. Liver disease severity alone does not fully predict high consumption of HRU, although when present, it is a predictor of high HRU.

848. Outcomes and Patterns of Health Care Usage among Acute Ischemic Stroke Patients in Canada

Anne-Marie Castilloux,[1] K. Tore Jørgensen,[2] F. Coste,[2] Yola Moride.[1,3] *[1]Yolarx Consultants, Montreal, QC, Canada; [2]Lundbeck, Valby, Denmark; [3]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada.*

Background: AIS is the second leading cause of death and a main cause of disability. Real-world data on outcomes and health care use are needed to support the value differentiation of new promising treatments.

Objectives: Characterize the Canadian AIS population (demographics, risk factors, medical history, and comorbidity); assess short-term (ST) and long-term (LT) outcomes (death and AIS recurrence), treatments, and healthcare use.

Methods: A retrospective cohort study was conducted using the Quebec prescription and medical services database. Incident AIS cases were identified with ICD-9 codes recorded in ER and hospital in 2011–2012. Patients were followed up for 1 year. Patient characteristics, medical history and risk factors were assessed in the year prior to event. Descriptive analyses were done, and Cox models were used to identify factors associated with outcomes. Since a high death rate was expected, a competing risk model was applied.

Results: We identified 6609 cases (49% male, 85% 65+ years old). During follow-up, 21% and 5% patients died during ST and LT periods, respectively, and 6% had a recurrence. Compared to 18–49 years old, older patients were at higher risk of dying (ST: HR = 3.8 (95%CI: 2.4–6.0) for 85+ years and 2.1 (1.4–3.4) for 75–84 years; LT: HR = 2.2 (1.1–4.5) for 85+ yrs). Presence of past medical conditions was a risk factor for death in ST and LT periods (HR = 1.5 (1.4–1.7) and 1.7 (1.4–2.2), respectively) and for AIS recurrence in LT period (HR = 1.6 (1.1–2.2)). Amongst drugs prescribed for AIS treatment (aspirin, clopidogrel, dipyridamole, and ticlopidine), aspirin was the most dispensed upon discharge (17% of patients) and remained the most dispensed during follow-up (47% of patients had 1+ aspirin disp.). During follow-up, 52% of patients had 1 + AIS-related test/procedure (mean: 1.3), 64% was hospitalised for 1+ day (mean 11) and 83%, 39%, and 83% had 1+ visit to GPs, cardiologist or other specialists resp. (mean 20, 3, and 18, respectively).

Conclusions: Age is a predictor of death following an AIS event. Age is not a predictor of AIS recurrence. Past medical conditions are a predictor for AIS

recurrence during LT period. Gender and patient's region are not predictive of death nor AIS recurrence.

849. Patterns of Health Care Utilization among Patients Hospitalized for Acute Ischemic Stroke (AIS) in Canada

Anne-Marie Castilloux,[1] K. Tore,[2] F. Coste,[2] Yola Moride.[1,3] *[1]Yolarx Consultants, Montreal, QC, Canada; [2]Lundbeck, Valby, Denmark; [3]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada.*

Background: Acute ischemic stroke (AIS) is the second leading cause of death worldwide and a main cause of disability. Real-world data on hospital healthcare usage in this population are needed to support the value differentiation of new and promising treatments.

Objectives: To characterize the population of patients hospitalized for AIS in Canada; to evaluate the use of in-hospital resources among AIS patients; and to characterize the place of discharge following hospitalization.

Methods: A cross-sectional study was conducted using the Discharge Abstract Database (DAD) of the Canadian Institute for Health Information (CIHI) and included all patients admitted for AIS (identified using ICD-10 codes) in eight of the 10 Canadian provinces in the years 2011–2012. Descriptive analyses were conducted on age, gender, province, risk factors for AIS, in-hospital resource use, and patient destination at discharge.

Results: A total of 38,580 hospital admissions for AIS were identified, which represents a rate of 0.09 per 100 person-years. Average length of stay was 10.5 days (SD: 14.5). Mean age of patients was 73 years (SD: 13.8), and men represented 51.7% of admissions. Hypertension, diabetes mellitus, and atrial fibrillation were the most common AIS risk factors (59.7%, 28.4%, and 21.8%, respectively). Death during hospitalization occurred in 11.6%. Places of discharge were home (32.8%), home with support service (11.5%), and long-term care facility (32.1%). The main stay during hospitalization was general medicine (54.3%) followed by neurology (33.5%). Of AIS patients, 47.0% had at least one procedure undertaken, the most common being computer tomography (38%).

Conclusions: DAD is a valuable data source for the assessment of patient characteristics and hospital resource use on a national basis. Males and females were evenly represented. Most patients were discharged in a home setting. Apart from computer tomography, patients had very few procedures.

850. A Descriptive Analysis of a Real-World Population with Chronic Hepatitis C (CHC) Treated with Simeprevir (SMV)-Based and/or Sofosbuvir (SOF)-Based Regimens: Findings from a US Payer Database

Jamie B. Forlenza,[1] Jonathan Fortier,[2] François Laliberté,[2] Patrick Lefebvre,[2] Neeta Tandon.[1] *[1]Janssen Scientific Affairs, LLC, Titusville, PA, USA; [2]Groupe d'Analyse, Ltée, Montréal, QC, Canada.*

Objectives: To provide real-world evaluations of newer direct-acting antivirals (DAAs) in CHC patients from large US payer perspectives.

Methods: Medical and pharmacy claims linked to lab data from the Humana database were analyzed for Medicare Advantage or commercially insured adults with 32 CHC claims (ICD-9 070.44; 070.54) who received therapy containing SMV and/or SOF through June 2014; those with HIV were excluded. Patients were grouped based on most common regimens in the data: SMV/SOF, SMV/SOF/ribavirin (RBV), SOF/RBV, or SOF/interferon (IFN)/RBV; <3% received other regimens. Baseline (BL) demographics and clinical characteristics (e.g., claims-based cirrhosis or end stage liver disease [ESLD], FIB-4 scores) were described, and post-treatment follow-up time measured. Methods to control for treatment selection bias were not performed, and comparative analyses were not conducted.

Results: There were 715 CHC patients who received therapy with SMV/SOF ($n=184$), SMV/SOF/RBV ($n=37$), SOF/RBV ($n=269$) or SOF/IFN/RBV ($n=225$); mean age was between 60 and 62 years; 58%, 68%, 62%, and 70% were male; most (85%, 78%, 81%, and 80%) had Medicare. For SMV/SOF, SMV/SOF/RBV, SOF/RBV, and SOF/IFN/RBV groups, BL cirrhosis was present in 27%, 27%, 17%, and 24% of patients and ESLD in 48%, 38%, 27%, and 12% of patients, respectively. Slightly over half in each cohort had calculable FIB-4 scores, of which, 56%, 54%, 34%, and 35%, respectively, had scores >3.25. Among those with genotype data, 100% (78/78) SMV/SOF, 94.7% (18/19) SMV/SOF/RBV, 24.4% (29/119) SOF/RBV, and 95.8% (92/96) SOF/IFN/RBV were genotype 1. Using prior claims history, 10%, 19%, 12%, and 17% of respective cohorts were treatment-experienced. Less than half of each cohort had post-treatment data ≥1 week.

Conclusions: This analysis of CHC patients predominantly insured through Medicare found that the majority of those who received SMV/SOF ± RBV had either cirrhosis or ESLD claims prior to therapy and, using lab data, over half had FIB-4 scores >3.25.

851. Pulmonologist Involvement and Overall Survival in Newly Diagnosed Extensive Stage Small Cell Lung Cancer Patients

Xinyi Ng,[1] Janaki A. Deepak,[2] Josephine Feliciano,[2] Amy J. Davidoff.[3] *[1]Department of Pharmaceutical Health Services Research, University of Maryland Baltimore, Baltimore, MD, USA; [2]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA; [3]Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA.*

Background: Despite well-established treatment regimens, overall survival (OS) of extensive stage small cell lung cancer (ES-SCLC) remains fairly poor. Pulmonologist management increases the probability of receiving active treatment, but there is limited evidence regarding the role of pulmonologists in OS of ES-SCLC patients.

Objectives: To assess whether pulmonologist involvement in the management of ES-SCLC is associated with improved OS.

Methods: In this retrospective study, newly diagnosed ES-SCLC cases between 2001 and 2005 were identified from the Surveillance Epidemiology and End Results-Medicare database. Pulmonologist involvement during the 6 months post-SCLC diagnosis is measured by the presence of ≥2 physician claims for an evaluation and management visit, with pulmonology reported as the physician specialty. Cox proportional hazard models stratified by receipt of recommended chemotherapy evaluated the effect of pulmonologist involvement on OS. To address potential bias due to reverse causality, we conducted two-stage residual inclusion (2SRI) instrumental variable analysis, with county level measures of pulmonologist visits for lung cancer patients as the instrument.

Results: Among 6009 ES-SCLC patients (mean age 75 years, 50% male), 15% received pulmonologist care and 42% received chemotherapy treatment. Median survival with and without pulmonologist care was 295 and 279 days among those treated ($p = 0.002$), and 112 and 73 days among those untreated ($p < 0.0001$). Pulmonologist involvement was associated with an 18% reduction in mortality risk among those who received chemotherapy [HR: 0.82; CI (0.74–0.91); $p < 0.0001$], and a 36% reduction in mortality risk among those who did not receive chemotherapy [HR: 0.64; CI (0.58–0.71); $p < 0.0001$]. After adjustment with the 2SRI model, pulmonologist involvement remained significantly associated with reduced mortality risk [HR: 0.57; CI (0.38–0.85); $p < 0.0001$] among the untreated patients.

Conclusions: Our findings demonstrated that pulmonologist involvement potentially improve OS in ES-SCLC patients. This supports a multidisciplinary approach emphasizing the role of pulmonologists in the management of ES-SCLC

852. Impact of Persistence and Adherence on Mortality in Women Treated with Hormonal Breast Cancer Therapy: A Nested Case Control Study in a French Nationwide Database

Pauline Bosco-Levy,[1,2,3] Annie Fourrier-Reglat,[1,2,3] Simone Mathoulin-Pelissier,[1,4,5] Nicholas Moore,[1,2,3] Julien Bezin.[1,2,3] *[1]Bordeaux University, Bordeaux, France; [2]INSERM, Clinical Epidemiology and Clinical Investigation Centre CIC1401, Bordeaux, France; [3]Centre INSERM U657-Pharmacoepidemiology, Bordeaux, France; [4]Clinical and Epidemiological Research Unit, Institut Bergonie, Bordeaux, France; [5]Centre INSERM U897-Epidemiology and Biostatistics, Bordeaux, France.*

Background: Non-persistence and non-adherence to oral hormonal anticancer drugs (tamoxifen or aromatase inhibitors) have been reported in women treated for hormone receptor-positive breast cancer (BC), but little is known about their impact on mortality.

Objectives: To evaluate the association of non-adherence and non-persitence of hormonal therapy in BC on mortality.

Methods: A retrospective cohort of women initiating an hormonal therapy between 2006 and 2008, surviving after the first year of treatment, and followed 5 years after initiation or until death was set up using reimbursement data of the French national healthcare insurance database (*Echantillon Généraliste de Bénéficiaires*, EGB). Within this cohort, a nested

case–control has been conducted to evaluate the impact on mortality of (i) hormonal therapy non-persistence (treatment discontinuation >90 days) and (ii) hormonal therapy non-adherence (medication possession ratio, MPR, <80%). Cases were defined as women who died from any causes during the study period. Controls (1 :3) were selected among those still alive at the date of cases death (index date) and matched on the onset date of treatment. Associations were assessed globally, for the first year of treatment and the year preceding the index date. Conditional logistic regression was used for analysis.

Results: A total of 125 cases and 374 controls were identified for the study. Globally, non-adherent (ORadj = 5.3, 95%CI [3.0, 9.6]) and non-persitent women (ORadj = 2.5, 95%CI [1.3, 4.9]) were more likely to die. This association was not found for the first year after treatment onset (non-adherence: 1.8, 95%CI [1.0, 3.4]); non-persistence: 0.7, 95%CI [0.2, 2.7]). Considering the year prior the index date, non-adherent women had a significant higher risk of death (ORadj = 4.1, 95% CI [1.3, 13.3]). No significant association was found for non-persistence (ORadj = 0.3, 95%CI [0.1, 3.2]).

Conclusions: This study showed that non-adherence and non-persistence to hormonal therapy may have an impact on mortality risk. However, the risk varies according to the time-window considered to measure adherence and non-persistence.

853. Persistence and Compliance with Lipid-Lowering Drugs in Patients with Chronic Kidney Disease

Viet Thanh Truong,[1,2] Jocelyne Moisan,[1,2] Edeltraut Kroger,[1] Serge Langlois,[3] Jean-Pierre Gregoire.[1,2] *[1]Chair on Adherence to Treatments, Faculty of Pharmacy, Laval University, Quebec, Canada; [2]Population Health and Optimal Health Practices Research Unit, CHU de Quebec Research Centre, Laval University, Quebec, Canada; [3]Faculty of Medicine, Laval University, Quebec, Canada.*

Background: As chronic kidney disease (CKD) progresses, the risk of cardiovascular diseases increases. For those who undertake a lipid-lowering drugs (LLD), persistence and compliance with LLD are important to benefit from the expected reduction in cardiovascular morbidity and mortality. Unfortunately, persistence and compliance with LLD have not been well studied in CKD patients.

Objectives: Our study aimed (1) to estimate the persistence with LLD 1 year after treatment initiation; (2) among those persisting, to estimate the compliance in the year following treatment initiation; and (3) to identify factors associated with persistence and with compliance.

Methods: Using Quebec administrative databases, we carried out a cohort study of individuals aged ≥18 who had started an LLD between 1 January 2000 and 31 December 2011. Individuals still undergoing treatment with any LLD 1 year after their first claim were considered persistent. Of these, we considered compliant those with a supply of drugs for ≥80% of days. We identified factors associated with persistence and with compliance using modified Poisson regression.

Results: Among 14,607 eligible individuals, 80.7% were persistent and 88.7% of these were compliant with their LLD. Individuals more likely to be persistent with LLD were patients with low (prevalence ratio: 1.03; 95%CI: 1.01–1.06) and medium socioeconomic status (SES) (1.04; 1.02–1.05) compared with those with high SES, patients treated by a nephrologist (vs. general practitioner) (1.06; 1.04–1.09), and patients who had hypertension (1.04; 1.02–1.06), diabetes (1.04; 1.03–1.06), stroke (1.09; 1.07–1.12) or coronary disease (1.07; 1.05–1.09). Individuals more likely to be compliant were patients aged ≥66 years (vs. 18–65) (1.04; 1.01–1.07), patients with low (vs. high) SES (1.08; 1.06–1.10), patients who used ≥12 (vs. <7) distinct drugs (1.03; 1.0–1.05), had been hospitalized (1.04; 1.02–1.06) or had stroke (1.04; 1.03–1.06).

Conclusions: One year after LLD treatment initiation, 28.4% of individuals with CKD were either no longer taking or had not been compliant with their treatment. Results could help target individuals who need help to better their LLD treatment.

854. The Adherence to Inhaled Drugs in COPD Patients: Effect on Survival

Valeria Belleudi,[1] Nera Agabiti,[1] Mirko Di Martino,[1] Silvia Cascini,[1] Ursula Kirchmayer,[1] Riccardo Pistelli,[2] Danilo Fusco,[1] Marina Davoli.[1] *[1]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [2]Department of Respiratory Physiology, Catholic University, Rome, Italy.*

Background: The debate on the effects on mortality of single or combined use of long-acting bronchodilators (LB) and inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) is still open. Few studies have examined how the continued use of inhaled medications affect survival.

Objectives: To assess the effect of adherence to LB/ICS therapy post-hospitalization for COPD on long-term mortality using a time-dependent approach.

Methods: The study is based on data from the information systems (hospitalization, drug, and mortality) of three Italian regions. A cohort of new users (45 + years) with a hospitalization for COPD in 2006–2009 and at least one prescription of respiratory drugs (R03) within 90 days after discharge was enrolled and followed for 5 years. Date of death was recorded. During the follow-up, for each subject, the daily use of LB and ICS was determined. Five levels of drug exposure time-varying were identified: adherent to LB/ICS, non adherent to LB/ICS, adherent to monotherapy LB, non adherent to monotherapy LB and inappropriate treatment (monotherapy ICS/other R03). Survival curves (Cox model) associated with the different treatments adjusted for baseline (socio-demographic, clinical severity, and previous COPD exacerbation) and time-dependent characteristics (COPD exacerbations, cardiovascular hospitalizations, and cardiovascular therapy) were evaluated.

Results: A total of 12 124 individuals surviving to 90 days post discharge for COPD were enrolled, mean age 73.8 years, 46% women. Follow up average time was 2.4 years, 3415 subjects had a death from natural causes in 5 years (mortality rate = 11.9 * 100 p.y.). Adherent to combination, LB/ICS had the highest probability of survival. In comparison to non adherent to LB/ICS, people adherent to monotherapy LB were more likely to survive (HR = 0.89; 95%CI 0.79–0.99). The lowest curve was found for the inappropriate treatment. Results were stronger in the subgroup with previous COPD exacerbations.

Conclusions: Adherence to therapy is essential for the effectiveness of treatment: early treatment after hospital discharge for COPD and keep the patient in appropriate treatment is just as effective and important the combined use of LB/ICS.

855. Comparative Adherence of ICS/LABA Products in Elderly Asthma Patients

Mina Tadrous,[1,2] Diana Martins,[2] Zhan Yao,[2] Matthew Stanbrook,[3] Samantha Singh,[2] David N. Juurlink,[2,4] Muhammad M. Mamdani,[1,2] Tara Gomes.[1,2] *[1]Li KaShing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [3]Division of Respirology, Department of Medicine, University Health Network, Toronto, ON, Canada; [4]Sunnybrook Research Institute, Toronto, ON, Canada.*

Background: Inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) combination products are commonly dispensed anti-inflammatory and bronchodilator agents used for the treatment of asthma. Limited evidence exists comparing the persistence between the ICS/LABA combination products budesonide/formetrol (BFC) and fluticiasone/salmetrol (FSC).

Objectives: To compare persistence of BFC to FSC therapy among new users in Ontario in patients 66 years of age and older using population-based administrative claims data.

Methods: We identified new users of ICS/LABA products among Ontario public drug beneficiaries aged 66 years and older between April 2008 and March 2013 with a maximum 2-year follow-up. Persistence to therapy was defined on the basis of a refill for the drug within a period equal to 150% of the prescription duration, and excluding individuals who received only one prescription. A Cox-proportional hazard model was used to analyze time to discontinuation, adjusting for differences in patient characteristics. Sensitivity analyses were conducted by varying the persistence definition.

Results: We found 8206 new FSC users and 3425 new BFC users. FSC users were found to be older (76.3 vs 74.7), more likely to use higher doses (39.4% vs. 2.3%), use more oral corticosteroids (23.8% vs 19.2%) and also have a diagnosis of COPD (72.6% vs. 62.6%). The median time to discontinuation was higher in FSC users (85 days) than the BFC users (70 days). Unadjusted and adjusted analyses found that BFC users were significantly more likely to discontinue therapy compared to FSC users (hazard ratio 1.16 (95%CI 1.10–1.21) and 1.07 (95%CI 1.02–1.13), respectively); however, this difference was small.

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Sensitivity analysis with a less conservative persistence definition found similar results.

Conclusions: The results suggest no difference between FSC and BFC in terms of persistence; the significance of the result is negligible and likely due to residual confounding within the population. This study supports prior studies that have suggested no difference in persistence between ICS/LABA combinations when used for the treatment of patients with asthma.

856. E-Monitoring of Asthma Therapy to Improve Compliance in Children (E-MATIC)

Erwin C. Vasbinder,[1,2] Lucas M.A. Goossens,[5] Hettie Janssens,[3] Brenda C.M. De Winter,[1] Liset Van Dijk,[4] Arnold G. Vulto,[1] Maureen P.M.H. Rutten,[5] Patricia M.L.A. Van den Bemt.[1] *[1]Hospital Pharmacy, Erasmus Medical Center, Rotterdam, The Netherlands; [2]Hospital Pharmacy, Groene Hart Ziekenhuis, Gouda, The Netherlands; [3]Division of Pediatric Respiratory Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; [4]NIVEL, Utrecht, The Netherlands; [5]Institute for Health Policy & Management, Rotterdam, The Netherlands.*

Background: Poor adherence to inhaled corticosteroids (ICS) is a risk factor for asthma exacerbations in children. Reminding systems are effective in adults.

Objectives: Main aim is to study the effect of real time medication monitoring (RTMM) with SMS reminders on adherence to ICS. Secondary aim is to study the effects on asthma control (AC), asthma-specific quality of life (QoL) and the frequency of exacerbations.

Methods: Design: multicenter, randomized controlled trial.

Study population: Children (4–11 years) from outpatient clinics of five Dutch hospitals, who use ICS for asthma.

Intervention: All children received RTMM for 12 months. The intervention group received SMS reminders, sent only when a dose was at risk of omission.

Main outcome measures: Primary outcome was adherence to ICS (% dosages taken in time). Secondary outcomes were AC (c-ACT), QoL (PAQLQ), and number of asthma exacerbations. Costs were calculated from a health care and from a societal perspective.

Statistical analysis: Adherence, AC, QoL and costs were examined using multilevel regression analysis for repeated measures. Adjusted means were calculated per measurement and over the full study period. The number of exacerbations was analysed using negative binomial regression. Uncertainty around the point estimates was assessed using bootstrapping.

Results: 209 patients were included. Mean age was 7.7 (SD 2.1) years. Adherence over full study period was 69.0% in the intervention group and 57.3% in the control group (difference 11.8%; 95%CI 6.9–17.5%). The difference declined from 15.2% during the first half year but remained stable at 8.3% over the last 6 months. There was no difference in AC at any time (mean c-ACT at the end of study 21.1 for intervention and 22.2 for control group), QoL (mean PAQLQ 6.2 vs 6.3) and exacerbations (yearly rate 0.23 vs 0.37). Costs were higher in the intervention group: €719 versus €615, a difference of €104 (95% CI: −€40 to €275) from the healthcare perspective and €1030 versus €743 from a societal perspective (difference €287, 95%CI: −€35 to €547).

Conclusions: RTMM with tailored SMS reminders effectively improves adherence to ICS, but not AC, QoL or exacerbations in this population.

857. Effects of Breast Cancer on Chronic Disease Medication Adherence in Elderly Women

Melissa L. Santorelli,[1,2] Hirshfield M. Kim,[4] Michael B. Steinberg,[3] Kitaw Demissie.[1,2,4] *[1]Rutgers Pharmacoepidemiology Program, Rutgers University, New Brunswick, NJ, USA; [2]Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA; [3]Internal Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA; [4]Cancer Control and Prevention, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA.*

Background: The effects of breast cancer diagnosis and management on chronic disease medication adherence in elderly patients remains largely unknown

Objectives: To determine the effects of breast cancer on chronic disease medication adherence among older women

Methods: The Surveillance, Epidemiology and End Results (SEER)–Medicare linked data and records from a 5% random sample of Medicare enrollees living in SEER areas were used. Stage I–III breast cancer patients who were ≥65 years of age in 2008 and women without cancer who were alive as of 31 December 2007

were eligible. Three distinct cohorts of medication users were identified: diabetes, hypertension and hyperlipidemia. For each cohort, breast cancer patients were frequency matched to four comparison women by age and geographic area. Prescription fills were assessed during a 2-year measurement period following baseline, which was defined as the diagnosis date for breast cancer patients and a randomly assigned date in 2008 for comparison women. Medication adherence was measured by the proportion of days covered (PDC) and medication persistence. A PDC of <0.8 defined non-adherence. Medication non-persistence considered the gaps that predicted long-term discontinuation

Results: The proportion of non-adherent subjects during the year prior to baseline was similar for women with and without breast cancer. During the post-baseline period, an elevated risk of diabetic medication non-adherence was observed for breast cancer as compared to comparison women [odds ratio (OR) = 1.41; 95% Confidence Interval (CI) = 1.05 to 1.89], while there was no significant difference between these groups in the risk of non-adherence to hypertensive (OR = 0.93; 95%CI: 0.76 to 1.12) and lipid-lowering medication (OR = 0. 94; 95%CI: 0.76 to 1.17). Women with breast cancer were also more likely [hazard ratio = 1.28; 95% CI: 1.02 to 1.62] to be non-persistent with diabetic medication relative to women without cancer

Conclusions: Special attention should be given in care planning, medication monitoring and coordination of primary care for elderly diabetic patients with a new diagnosis of breast cancer

858. Primary Non-Adherence to Antidepressants: Differences by Class

Heather D. Anderson,[1] Gerald E. Pulver,[2] Sam L. Ellis,[1] Mykel G. Walsh,[1] John T. Lynch,[3] Robert J. Valuck.[1] *[1]Clinical Pharmacy, University of Colorado Denver Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA; [2]Family Medicine, University of Colorado Denver School of Medicine, Aurora, CO, USA; [3]Connecticut Center for Primary Care, Inc., Farmington, CT, USA*

Background: Antidepressants (AD) are effective in treating depression and other disorders. However, up to 30% of patients do not fill their prescription (i.e., primary non-adherence) within a year of it being issued. While the effectiveness of AD classes is similar, side effect profiles, and consequently adherence, may be different. Primary non-adherence to specific classes of antidepressants is unknown.

Objectives: Estimate and compare primary non-adherence across AD classes using varying time-to-fill criteria. **Methods:** Adult patients (age 18+ years) with a new AD prescription in 2010–2012 were identified from the Connecticut Center for Primary Care electronic health record database, which contains over 250,000 adult patients. Prescriptions were linked to pharmacy fill records at the medication-level. ADs were classified as selective serotonin reuptake inhibitors (SSRI), selective-norepinephrine reuptake inhibitors (SNRI), tricyclics (TCAs), and all others combined. Primary non-adherence was expressed as the percent of patients with a prescription who did not fill the medication within 30, 180, or 365 days. Risk ratios (RR) adjusted for year of prescription were estimated to compare primary non-adherence across AD classes.

Results: A total of 23,495 patients received a new AD prescription from 2010 to 2012. Primary non-adherence was 57% (30 days), 44% (180 days), and 38% (365 days). Thirty-day primary non-adherence was best for SSRIs (57%) and worst for SNRIs (61%). Patients were significantly less likely ($p < .05$) to fill SNRIs within 30 days compared to SSRIs (RR = .94), TCAs (RR = .90), and other antidepressants combined (RR = 0.90). Median time-to-fill was 0 days; mean time-to-fill was 2 days for fills within 30 days and 56 days for fills within 365 days.

Conclusions: More than 50% of adults who received an AD prescription did not fill it within 30 days. Prescribers should be aware of the high rate of primary non-adherence to ADs, particularly SNRIs, and assess patients for primary non-adherence within 30 days following a new prescription. Decreasing primary non-adherence will ultimately increase the number of patients taking effective medication to treat their disorder.

859. Validity of Pharmacy-Based Adherence Measures in Individuals with Type 2 Diabetes

Arsène Zongo,[1,3] Jocelyne Moisan,[1,2,3] Jean-Pierre Grégoire,[1,2,3] Line Guénette.[1,2,3] *[1]Faculty of Pharmacy, Université Laval, Québec, QC, Canada; [2]Chair on Adherence to Treatments, Université Laval, Québec, QC, Canada; [3]Population Health and Optimal Health Practices Research Unit, CHU de Québec Research Centre, Québec, QC, Canada.*

Background: Suboptimal adherence to antidiabetes drug treatment is a critical issue that calls for proper assessment methods. Pharmacy-based data are frequently used in pharmacoepidemiology, yet their validity in assessing adherence when >1 antidiabetes drug is being prescribed is unknown.

Objectives: To assess the validity of pharmacy-based adherence measures in a population of individuals with type 2 diabetes (T2D) prescribed ≥1 class of antidiabetes drugs.

Methods: A convenience sample of 92 T2D patients of the Canadian province of Quebec provided a measure of HbA1c. Four different adherence measures were computed using patients' 3-month drug refills data: (1) the [mean] proportion of days covered (PDC) by drugs of each class, (2) the proportion of days with ≥1 class of drugs available, (3) the proportion of days with all classes of drugs available, and (4) the daily [poly]pharmacy possession rate (DPPR). For each measure, adherence was defined using two different cut-offs (≥70% and ≥80%). We examined the association between each adherence measure and an HbA1c >7% using log-binomial regressions.

Results: Sixty-three participants (68.5%) were using ≥2 classes of antidiabetes drugs. At the 70% cut-off, the risk ratio (95%CI) of an HbA1c >7% adjusted for diabetes duration was 1.34 (0.95–1.92), 1.23 (0.85–1.78), and 1.65 (1.17–2.32), for the mean PDC, the proportion of days with all classes available, and the DPPR, respectively. Note that at this cut-off, the risk ratio related to the proportion of days with ≥1 class available could not be computed as one cell had a null value. At the 80% cut-off, risk ratios were non-statistically significant.

Conclusions: Results suggest that the DPPR is the more accurate mean to compute pharmacy-based adherence to T2D treatment when ≥1 class of drugs is prescribed to patients. Attention should be paid to cut-off point used to define adherence.

860. Persistence of Proton Pump Inhibitor Refills in Community Pharmacies

Emre Yucel,[1] Aylin Yucel,[2] Latif Ozbay.[3] *[1]School of Public Health, University of Texas at Houston, Houston, TX, USA; [2]College of Pharmacy, University of Houston, Houston, TX, USA; [3]College of Pharmacy, Yeditepe University, Istanbul, Turkey.*

Background: Adverse reactions due to inappropriate and long-term use of proton pump inhibitors (PPIs) reported in several studies such as drug-drug interactions with concomitant use, clostridium difficile infections, hypomagnesemia, calcium malabsorption and bone fracture risk. Persistence analysis is needed to understand prevalence of long-term PPI use in the community. More research is needed to identify PPI 'long term use'.

Objectives: The overall aim of the investigation is to explore the persistence to PPI prescriptions by Turkish patients in terms of their duration of use through prescription refills at community pharmacies. The primary aim was to evaluate the prevalence of persistence of one time and more prescription use of PPIs with the covariates of age, gender, pharmacy location and PPI type.

Methods: In this retrospective cross-sectional study, we identified a claims database with 1977 patients on PPI therapy from two community pharmacies located in Yalova, Turkey. We defined persistence as the time from the initial filling of prescription until discontinuation of refilling that prescription within the study period [1/1/2011 to 31/1/2012 (13 months)]. Lag function and a permissible gap, which has a range of 14 days, were deployed. Logistic regression was used for persistence of once and more, and persistence of twice and more.

Results: There were 1004 patients who filled at least one prescription entailing at least one proton pump inhibitor during the period selected. Four hundred fifty-four (45.22%) of these patients filled his/her prescription at the central pharmacy and 550 (54.78%) at the peripheral pharmacy. Men have 44% less the odds of refilling a PPI entailing prescription more than once as compared to women, controlling for all other covariates, assuming no bias and no confounding. Patients who are visiting the peripheral pharmacy have 17.5% less the odds of refilling their prescriptions more than once (persistence more than once) as compared to the central pharmacy

Conclusions: Persistence for therapy for long-term PPI use over recommended period is prevalent (85% of prescriptions). The implications of inappropriate and long-term PPIs could lead to loss of efficacy in this patient population with added risks

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861. Liver Outcomes and Mortality among Patients Newly Diagnosed with Hepatitis C Virus Infection in Israel during the Period 2006–2011

Clara Weil,[1] David R Walker,[2] Varda Shalev,[1,3] Mira Friedman,[1,3] Gabriel Chodick.[1,3] *[1]Medical Division, Maccabi Healthcare Services, Tel Aviv, Israel; [2]Health Economics and Outcomes Research, Abbvie, North Chicago, IL, USA; [3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.*

Background: Hepatitis C virus (HCV) is a leading cause of chronic liver disease including cirrhosis, liver cancer and complications of end-stage liver disease. While the incidence of HCV is declining in many areas, morbidity and mortality are expected to increase among patients infected decades ago.

Objectives: This study aimed to assess real-world liver-related health outcomes and all-cause mortality (ACM) among treated and untreated patients newly diagnosed with HCV.

Methods: The study used the databases of Maccabi Healthcare Services, a 2-million-member HMO in Israel. Chronic HCV infection was defined by a positive PCR test for HCV RNA and HCV genotype testing. Included were adults first diagnosed with HCV during 2006–2011 (index period).Patients were classified as "treated" if they initiated HCV treatment (peg-interferon and ribavirin) during the index period and "adherent" based on the proportion of days covered (≥80%) with interferon from pharmacy records. To address immortal time bias, follow-up began at treatment onset (median = 6 months post-diagnosis) or, for untreated patients, at 6 months post-diagnosis. Outcomes measured through June 2013 included hepatocellular cancer, hepatic failure, and liver transplant (as a composite liver outcome, CLO) and ACM.

Results: We identified 2208 newly diagnosed patients (59% male; mean age, 44 years). Genotype 1 was predominant. Less than 50% of patients started treatment during the index period. CLO occurred in 1.6 per 1000 person-years. In a multivariable analysis, the risk for CLO was over five times higher ($p < 0.05$) among patients with baseline cirrhosis compared to non-cirrhotics, and among patients with chronic kidney disease (CKD) compared to non-CKD patients. Compared to adherent patients, the adjusted hazard ratios for ACM were over twice as high among untreated and non-adherent patients ($p < 0.05$).

Conclusions: Study results indicate that adherence to interferon-based HCV treatment following diagnosis of HCV is associated with reduced all-cause mortality. This highlights the urgent need for early diagnosis and treatment of HCV.

862. Adherence to Interferon-Based Treatment among Patients Newly Diagnosed with Hepatitis C Virus in Israel during the Period 2006–2011

Clara Weil,[1] David R Walker,[2] Varda Shalev,[1,3] Mira Friedman,[1,3] Gabriel Chodick.[1,3] *[1]Medical Division, Maccabi Healthcare Services, Tel Aviv, Israel; [2]Health Economic and Outcomes Research, Abbvie, North Chicago, IL, USA; [3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.*

Background: Infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide. Adherence to pegylated interferon and ribavirin is a major challenge due to significant adverse events and, while new treatments are being developed, it remains important to assess current interferon-based regimens.

Objectives: This study aimed to assess real-world adherence and effectiveness among patients with recently diagnosed and treated HCV infection.

Methods: The study used the databases of Maccabi Healthcare Services, a 2-million-member HMO in Israel. Chronic HCV infection was defined by a positive PCR test for HCV and genotype testing. Included were adults first diagnosed with HCV infection and treated (peg-interferon and ribavirin) during 2006–2011; patients were followed through June 2013. We measured discontinuation (treatment gap ≥60 days) and adherence (i.e. proportion of days covered ≥80%) using dispensed interferon from pharmacy records and accounting for recommended treatment duration. Sustained viral response (SVR) was assessed using PCR tests within a year of the end of treatment.

Results: We identified 872 newly diagnosed and treated patients (61% male; mean age, 41 years). Genotype (G) 1 was predominant. Approximately 20% discontinued treatment early, after a median of 16 and 8 weeks for G1/4 and G2/3, respectively. Over 75% of patients were adherent. Adherence was significantly more likely among G2/3 compared to G1/4 patients (OR = 2.9) and

among never-smokers compared to ever-smokers (OR = 1.9). Overall, half of patients attained SVR. While SVR rates were lower for G1/4 than for G2/3 (70% vs. 86%), adherent patients had higher SVR rates compared to non-adherent patients (67% vs. 14%).

Conclusions: Patients with HCV G1 were significantly less likely to be adherent and to attain SVR, compared to G2/3. Adherence to interferon-based regimens is a strong predictor of SVR, and further research is needed to assess how patient care programs can improve adherence among diverse populations, and to understand implications for new HCV treatment regimens.

863. Determinants of Patient Adherence to Imatinib – A Retrospective Study in a Malaysian Teaching Hospital

Sharmini Balashanker,[1] Li-Chia Chen,[2] Chelsea AM Taylor,[1] Siew Siang Chua,[3] Izam EM Zakaria.[4] *[1]School of Pharmacy, University of Nottingham, Semenyih, Selangor, Malaysia; [2]School of Pharmacy, University of Nottingham, Nottingham, UK; [3]Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [4]Pharmacy Department, University Malaya Medical Centre, Kuala Lumpur, Malaysia.*

Background: Suboptimal adherence to imatinib, an oral anticancer agent, has been found to be significantly associated with negative clinical outcomes and increase in health care costs. The multi-factorial determinants of non-adherence to imatinib have not been studied in Malaysia.

Objectives: This study aimed to identify demographic, social and medication related factors that influenced the adherence to imatinib.

Methods: This retrospective cohort study was conducted in a major teaching hospital in Malaysia using prescription fill data.

All patients who filled at least two prescriptions of imatinib from July 2009 to December 2012 were included. Patients were followed from the imatinib index date until the last day of imatinib supply or until the end of the study period. Patients' imatinib supply details throughout the study period were collected. Patients' demographic data as well as access to funding at their imatinib index date were also recorded.

The medication possession ratio (MPR) of imatinib was used as a proxy to evaluate adherence. The duration of imatinib supply and cumulative number of concomitant medicines were also evaluated.

Data were analysed using descriptive statistics and multiple regression analysis.

Results: A total of 100 patients (61% male; mean age 45.8 ± 19.9 years) were included, and the mean follow-up duration was 0.99 (range 0.04 to 3.03) patient-years. The MPRs of 72 patients were ≥80%, and 58 patients used concomitant medicines (range 1 to 38). The mean MPR was 88.0 ± 22.3%, and only significantly associated with duration of imatinib supply ($p = 0.022$). For the 32 patients with five or more concomitant medicines, the mean MPR was significantly higher in those aged 60 or more (96.9% vs. 82.6%, $p = 0.041$).

Conclusions: The MPR of imatinib is not significantly associated with age, gender, ethnicity, employment status or access to funding in this study. The number of concomitant medicines impacts upon the MPR of the younger population, which suggests that this group of patients may need more support to enhance their adherence to imatinib therapy.

864. Development of a New Methotrexate (MTX)-Specific Adherence Tool for Use in the Management of Patients with Rheumatoid Arthritis (RA)

Jeffrey R Curtis,[1] Maher Aassi,[2] Carla Dias Barbosa,[3] Corrado Bernasconi,[2] Michel Brethous,[2] Benoit Arnould.[3] *[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]F. Hoffmann-La Roche, Basel, Switzerland; [3]Mapi HEOR, Lyon, France.*

Background: Despite the development of biologics for the treatment of rheumatoid arthritis (RA), MTX remains the preferred initial antirheumatic drug (Smolen, *Ann Rheum Dis* 2010). Evidence shows patient adherence to RA medications is suboptimal (Pasma, *Semin Arthritis Rheum* 2013).

Objectives: To develop a self-administered tool to assess patient adherence to MTX for use in research and clinical practice to help clinicians make better-informed treatment decisions.

Methods: Thirty-two face-to-face interviews were conducted in the USA with RA patients currently or

previously treated with MTX. Interviews were recorded with patient permission, transcribed verbatim, and analyzed using ATLAS.ti software. Qualitative analysis of transcripts included sorting quotes based on adherence-related concepts, organizing them into homogeneous domains based on theoretical models of health-related behavior, and creating a conceptual model. A saturation review was conducted to verify that all significant concepts were captured.
Results: The median age of interviewed patients was 57 years, and 68% were women. Of 32 patients, 11 were receiving oral MTX, 15 were receiving an injectable form of MTX, and six had stopped MTX at the time of the interview. Of 26 patients receiving MTX, 21 were taking MTX in combination with other RA therapies. The conceptual model resulting from the interviews was discussed with clinical experts, and relevant adherence concepts specific to MTX were selected. For each relevant concept, ≥1 item was generated using words collected during interviews. A test version of the new adherence tool was developed with 30 items covering practical barriers to MTX (5 items), patient behavior related to MTX (9 items), perceived efficacy of MTX (six items), perceptual and emotional barriers related to MTX (7 items), and patient opinions about care (three items).

Conclusions: This new MTX adherence tool will be pilot tested with patients and clinicians for comprehension and relevance and subjected to further assessment, modification, and validation to ensure its robustness in assessing MTX adherence in research and clinical practice.

865. Medication Adherence in Chronic Myeloid Leukemia and Patients' Need for Information

Christel Boons,[1] Lonneke Timmers,[1] Jeroen Janssen,[2] Jan de Jong,[3] Eleonora Swart,[1] Jacqueline Hugtenburg.[1]
[1]Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam, The Netherlands; [2]Hematology, VU University Medical Center, Amsterdam, The Netherlands; [3]Stichting Contactgroep Leukemie, Utrecht, The Netherlands.

Background: The efficacy of the tyrosine kinase inhibitors (TKI) imatinib, dasatinib, and nilotinib has changed chronic myeloid leukemia (CML) from being a progressive fatal disease to a chronic condition. With the indefinite use and associated side effects, poor adherence has been recognized as the most important determinant of treatment failure in CML.

Objectives: The aim of the study was to get insight into drug taking behaviour and patients' needs for information.

Methods: In this cross-sectional study, carried out in April to May 2013, a questionnaire was sent to 185 CML patients through the Dutch leukemia patients group. The questionnaire included the items treatment concern, adherence, and patients' need for information.
Results: A total of 73 patients (43% male, 54 ± 12 years) responded, of whom 16% were off-treatment, 44% on imatinib, 14% on dasatinib, and 26% on nilotinib. Twenty-five percent (15/61) of patients on-treatment reported to miss an intake at least once a month (one patient twice a month). Reasons are they forget (47%), intentionally skipping (33%), or both forgetting and intentionally skipping doses (20%). Nine of these patients (60%) stated no concerns about missing an intake. Most patients (87%) were satisfied about the information provided. The physician (69%), the Internet (59%), and the Dutch leukemia patients group (20%) were reported as the main sources. Fifty-six patients (92%) wanted to have more information on the following: side effects (73%), CML (64%), TKI effect (48%), quality of life (39%), use of the TKI (21%), and medical advances (14%).

Conclusions: A considerable part of the CML patients was not fully adherent. Although most patients were generally well satisfied about the information received, a need for more information was obvious. Interventions to improve the use of TKI in CML should include comprehensive patient information.

866. Trajectories of Adherence to Thienopyridines after Coronary Stenting in Patients on Dialysis

Jenny I. Shen,[1] Tara I. Chang,[2] Maria E. Montez-Rath,[2] Wolfgang C. Winkelmayer.[3] *[1]Harbor-UCLA Medical Center, Torrance, CA, USA; [2]Stanford University School of Medicine, Palo Alto, CA, USA; [3]Baylor College of Medicine, Houston, TX, USA.*

Background: Adherence to medications often fluctuates over time.

Objectives: To identify different trajectories of adherence to thienopyridines after percutaneous intervention (PCI) with stenting in patients on dialysis and evaluate the associations with cardiovascular (CV) outcomes.

Methods: We identified from the United States Renal Data System (USRDS) all adult maintenance dialysis patients with Medicare Parts A, B, and D who had PCI with stenting from 7/2007 to 12/2010. Using group-based trajectory modeling (PROC TRAJ), we classified patients by their pattern of adherence to thienopyridines in the 6 months after discharge, excluding patients who had a CV event during that period. We used Cox regression to estimate the hazard ratio (HR) for the composite outcome of death, myocardial infarction, or repeat revascularization associated with each trajectory.

Results: Among 4948 patients, we identified four trajectories of adherence: (1) consistent high adherence; (2) high adherence with gradual decline; (3) moderate adherence with gradual improvement; and (4) moderate adherence with rapid decline.

In multivariable analyses, we found no significant differences in the risk of the composite outcome among the four trajectories:

Trajectory (vs. group 1), HR (95% confidence interval):

2, 1.04 (0.94–1.16)
3, 1.06 (0.93–1.20)
4, 1.07 (0.96–1.19)

Conclusions: Among dialysis patients, four major trajectories of adherence to thienopyridines in the 6 months post-discharge for PCI were identified. However, none was associated with a higher risk of the composite CV outcome than the others. Adherence to thienopyridines may not be effective in preventing CV outcomes post-PCI in dialysis patients. Further studies are needed to better guide clinical practice.

867. Preliminary Analyses of Primary Adherence and Persistence to Antihypertensive Therapy in Portuguese Primary Care Units

André F. Coelho, Pedro A. Caetano.

Pharmacy, Lisbon School of Health Technology, Lisbon, Portugal; Phamacology, NOVA Medical School, Lisbon, Portugal.

Background: Non-adherence to antihypertensive therapy is mostly relevant in the case of a recent diagnosis or prescription of new antihypertensive drugs, being estimated that up to 30% of patients fail to initiate therapy and up to 50% discontinue it during the first year of treatment.

Objectives: To determine primary adherence and persistence to antihypertensive therapy in newly treated hypertensive patients with a single antihypertensive drug in primary care units from within the Lisbon region in Portugal.

Methods: We are conducting an observational retrospective cohort study. Study population consists in all newly diagnosed and treated hypertensive patients in the primary care units within Lisbon area during first trimester of 2011. Prescription and claims data were collected for a 2-year follow-up after index date and a run-in period of 6 months. For this preliminary analysis, we have selected patients treated with a single drug. Primary adherence was quantified as the proportion of patients not exceeding 180 days after index prescription to pharmacy acquisition. Persistence was quantified as the proportion of patients still engaged with their treatment during follow-up using a Kaplan–Meier analysis.

Results: Patients treated with a single drug represent 68.6% of the cohort. Mean age is 66.6 ± 12.5 years and 58.5% are male. Almost three-fourth of the prescriptions were of an agent acting on the renin–angiotensin system and of those, 56.6% represent a combination pill. Thirty-five percent of patients were classified as primary non-adherents. Primary non-adherence was more common for patients receiving a calcium channel blocker or a beta blocking agent. Only 25.8% remain engaged with their treatment after 2 years. Thirty percent of non-persistent patients demonstrate an early discontinuation. Greater class persistence was observed to agents acting on the renin–angiotensin system, as compared to diuretics ($p < 0.01$).

Conclusions: This preliminary analysis demonstrates a relatively low medication adherence rate to antihypertensive therapy in Portugal. Newly diagnosed and treated patients should therefore be monitored carefully to increase their adherence and, thus, their hypertension control.

868. Use of the Guideline-Recommended Drugs after a First Acute Myocardial Infarction in the Province of Québec in the Elderly: Effect of Deprivation and Sex

Adjo E Akator,[1,2] Claudia Blais,[2,1] Phillipe Gamache,[2] Guénette Line.[1] [1]*Faculté de Pharmacie, Université*

Laval, Québec, QC, Canada; [2]Surveillance des Maladies Chroniques, Institut National de Santé Publique du Quebec, Québec, QC, Canada.

Background: In Quebec, Canada, people with low socioeconomic status (SES), measured with a deprivation index, have higher mortality in the year following their first acute myocardial infarction (AMI) compared to those with higher SES. Differences in cardiac procedures were not the source of this inequality.
Objectives: To evaluate whether there are differences in the use of the guideline-recommended drugs (GRD) following a first AMI in elderly people according to their SES and sex, knowing that the vast majority are covered by the public drug plan.

Methods: We conducted a population-based cohort study of people aged ≤65 years living in Quebec using the Quebec Integrated Chronic Disease Surveillance System (QICDSS). Individuals having a first hospitalized AMI between 1 January 2006 and 31 December 2011 and being covered by the public drug plan 6 months before and at least 30 days following this hospitalization were considered. People were deemed using the GRD if they received simultaneously drugs from at least three classes (antiplatelet, beta-blocker, and statin) on the 30th and the 365th day after hospital discharge. Associations between use of drugs, SES, and sex were estimated with multivariate logistic and log-binomial regressions according to other covariates.

Results: On day 30 and 365, after hospital discharge respectively 19,017 and 16,547 individuals were considered among which 13,234 (69.6%) and 10,772 (65.1%) were using GRD. No significant association was observed for most materially and socially deprived compared to least deprived: material relative risk (RR) = 1.02, 95% confidence interval [CI], 0.96–1.09 and RR = 1.03, 95%CI, 0.97–1.10; social RR = 1.00, 95%CI, 0.94–1.07, and RR = 1.00, 95% CI, 0.96–1.05, respectively, while it was significant only at 30 days for men (RR = 1.08, 95%CI, 1.03–1.12).

Conclusions: Regardless of their SES, our results suggest equitable access and drug use for the elderly in the public drug plan that experienced a first AMI. Higher mortality of people with low SES in the year following their first AMI is likely not attributable to poorer drug use. Other hypotheses should be studied.

869. Patterns of Statin Use Following Initiation of Lipid Lowering Therapy in a Commercial Insurer's Administrative Database

Florence T Wang,[1] Ling Li,[1] Laura Yochum,[1] Ben Taylor,[2] Robin Clifford,[1] John D Seeger[1,3] *[1]Epidemiology, Optum, Waltham, MA, USA; [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, USA; [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA.*

Background: Statins are commonly prescribed to treat hypercholesterolemia and prevent heart disease, yet patterns in statin use and adherence remain incompletely described.

Objectives: To describe patterns of statin use in the first year after therapy initiation within a US commercial health insurer's administrative database.

Methods: New users of statin and other lipid lowering therapy were identified from the database from 2009 to 2012. On a quarterly basis, we described patterns of statin use including dose and changes in the statin regimen including up-tiltration or down-titration, switching, and discontinuation of therapy. Low-density lipoprotein cholesterol (LDL-C) values within 14 days were summarized, as available, within the quarters as well.

Results: Of the 483,902 statin initiators, 59% started with a low potency statin (median LDL-C at initiation: 149 mg/dl). At 3, 6, 9, and 12 months post therapy initiation, 48%, 50%, 53%, and 54%, respectively, had discontinued statin therapy. Comparing statin use across quarters among those who continued on statin therapy, the majority (range 66–92%) of users remained on the same statin regimen, while 1–2% down-titrated and 2–5% up-titrated their statin therapy. Following initiation, the median LDL-C of statin initiators (irrespective of discontinuation status) was 100 and 90 mg/dl for those who remained on statins. Of the 72,329 initiators of lipid-lowering therapy other than statins (median LDL-C at initiation: 117 mg/dl), 39% remained on other lipid lowering therapy and 4% was on statin therapy at 3 months after initiation, while 29% remained on other lipid lowering therapy and 9% were on statin therapy at 1 year. Following initiation, the median LDL-C among initiators of other lipid-lowering therapy (irrespective of discontinuation status) was 111 mg/dl as compared with 93 mg/dl for the subset

who switched to statin therapy. Across both cohorts, there was little switching between the generic statins.

Conclusions: Persistence to lipid-lowering therapy may be low, with over 50% of statin initiators and 60% of initiators of other lipid-lowering therapy discontinuing use within 3 months of therapy initiation.

870. Factors Influencing Adherence and Persistence to Cardiovascular Medications: A Systematic Review

Danielle M van der Laan,[1,2] Petra JM Elders,[2,3] Christel CLM Boons,[1] Giel Nijpels,[2,3] Jacqueline G Hugtenburg.[1,2] *[1]Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam, The Netherlands; [2]EMGO Institute for Health and Care Research, Amsterdam, The Netherlands; [3]General Practice and Elderly Care Medicine, VU University Medical Center, Amsterdam, The Netherlands.*

Background: Medication non-adherence is a complex healthcare problem. Due to medication non-adherence, a substantial number of cardiovascular (CV) patients benefit from their medication to a limited extent. Understanding the complexity of adherence and its influencing factors is important for the development of interventions that adequately address non-adherence.

Objectives: A systematic literature review was performed aimed at providing an overview of factors influencing adherence and persistence to CV medication

Methods: Medline, Embase, PsycINFO and The Cochrane Library were searched for studies focusing on factors influencing (non)-adherence and (non)-persistence to CV medication, published until August 2014. Titles, abstracts and full texts were reviewed independently by two researchers according to predetermined inclusion criteria. Factors were classified according to the World Health Organization (WHO) multidimensional adherence model.

Results: After reviewing 357 articles in full text, 160 articles were eligible for quality assessment. After excluding 14 studies due to weak methodological quality, 146 studies of moderate to strong quality were included and systematically reviewed. A wide variety of factors covering all five WHO dimensions were found to influence non-adherence and non-persistence. Factors most commonly associated with non-adherence and non-persistence were as follows: poor knowledge; poor health literacy; more negative beliefs about medication; unhealthy lifestyle; poor cognitive health; racial/ethnic minority status; perceived discrimination; lower educational level; and communication problems between patient and prescriber.

Conclusions: Medication adherence and persistence are influenced by multiple factors. However, the results must be interpreted with caution due to the methodological heterogeneity of the studies included. There is no clearly defined profile of non-adherence in CV patients. Therefore, a one-size-fits-all approach in designing interventions to address this problem is no longer appropriate. Only when interventions are specifically tailored to the needs of individual patients, higher adherence rates can be achieved.

871. Factors Associated with Non-Adherence to Cardiovascular Medication: A Comparison between Pharmacy Refill and Self-Report Methods

Danielle M. van der Laan,[1,2] Petra J.M. Elders,[2,3] Christel C.L.M. Boons,[1] Giel Nijpels,[2,3] Jacqueline G. Hugtenburg.[1,2] *[1]Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam, The Netherlands; [2]EMGO Institute for Health and Care Research, Amsterdam, The Netherlands; [3]General Practice & Elderly Care Medicine, VU University Medical Center, Amsterdam, The Netherlands.*

Background: Adherence to cardiovascular (CV) medicines is influenced by multiple factors. There are several ways to assess adherence, but no method is universally accepted. Objective methods seem to provide the best measure of adherence. However, they are not always available and mainly assess medication refill behaviour. Subjective methods provide information about medication intake behaviour but are prone to bias.

Objectives: The aim is to provide more insight into factors associated with non-adherence and their potential variability as related to the use of different adherence assessment methods.

Methods: Adherence to CV medication was assessed using two methods: pharmacy refill data and patient self-report. Patients were asked to complete a comprehensive questionnaire covering potential factors for non-adherence, for example, demographic characteristics, medication-related beliefs, and quality of life. Logistic regression analyses were used to assess the association of factors with non-adherence. Results obtained with both methods were compared.

Results: In total, 255 patients participated in the study. Depending on the method used, 42% (pharmacy refill) and 70% (self-report) were identified as non-adherent. Factors significantly associated with both pharmacy refill and self-reported non-adherence were of younger age, had difficulties with intake due to forgetting, had lower positive necessity-concern differential (i.e., perception that benefits of medicines outweigh costs), and having an ambivalent attitude towards medicines. Pharmacy refill non-adherence was also associated with lack of knowledge on what to do when forgetting to take medicines. Self-reported non-adherence was specifically associated with worries about side effects, more concerns about medicines, and lack of knowledge on medicine effects.
Conclusions: Assessment of non-adherence by means of self-report seems to overestimate the problem. Overlap in associated factors was seen, but variability of factors between the different methods was also observed. When developing interventions to improve adherence, the method-related variability in adherence associated factors must be taken into account.

872. Primary Non-Adherence Associated with Rosuvastatin from Electronic Health Record (EHR) Prescribing Data in the United States

Christopher G. Rowan,[1] Nikita Stempniewicz,[1] James Flory,[2] Tobias Gerhard,[3] James D. Lewis,[4] John Cuddeback,[1] Sean Hennessy.[4] *[1]American Medical Group Association, Alexandria, VA, USA; [2]Weill-Cornell School of Medicine, New York, NY, USA; [3]Ernest Mario School of Pharmacy, Piscataway, NJ, USA; [4]University of Pennsylvania, Philadelphia, PA, USA.*

Background: Primary non-adherence (PNA) is a significant therapeutic problem among patients with hyperlipidemia. PNA occurs when patients who are prescribed a medication fail to fill the prescription at the pharmacy. The linkage between electronic health records (EHR) prescribing (Rx) data and pharmacy claims data provides a unique opportunity to study PNA.

Objectives: The purpose was to describe the proportion of patients with an ambulatory rosuvastatin EHR Rx (within medical groups that consistently using e-prescribing) where there is no corresponding pharmacy claim for rosuvastatin.

Methods: A retrospective cohort study was conducted to evaluate PNA. The study population was extracted from the Optum Labs Data Warehouse (OLDW), which contains de-identified administrative claims and EHR data. We included patients who had both (linked) claims (with a pharmacy benefit) and EHR data in 2012. Among patients with an ambulatory rosuvastatin EHR Rx, we determined the probability of not having a pharmacy claim for rosuvastatin within 1, 3, 6, and 12 months following the last rosuvastatin EHR Rx in 2012. We stratified this analysis by patients with an incident versus prevalent EHR Rx for rosuvastatin.

Results: A total of 5486 patients had an EHR Rx for rosuvastatin, 60% of whom had an EHR Rx for rosuvastatin in the prior year (prevalent cohort). Among all patients, PNA within 1, 3, 6, and 12 months of the rosuvastatin EHR Rx was 33%, 23%, 20%, and 19%, respectively. For patients with an incident rosuvastatin EHR Rx, PNA was 37%, 28%, 26%, and 24%. For the prevalent cohort, PNA was 28%, 19%, 17%, and 16%.

Conclusions: One third of patients do not fill their rosuvastatin prescription in the first month. By 12 months, about 20% still had not filled their prescription. Patients with an incident rosuvastatin prescription have worse PNA, by 8–9%, compared to those with a prevalent rosuvastatin prescription. Armed with these findings, healthcare providers

873. Medication Possession Ratio Associated with Rosuvastatin from Electronic Health Record (EHR) Prescribing Data in the United States

Christopher G. Rowan,[1] Nikita Stempniewicz,[1] James Flory,[2] Tobias Gerhard,[3] James D. Lewis,[4] John Cuddeback,[1] Sean Hennessy.[4] *[1]American Medical Group Association, Alexandria, VA, USA; [2]Weill-Cornell School of Medicine, New York, NY, USA; [3]Ernest Mario School of Pharmacy, Piscataway, NJ, USA; [4]University of Pennsylvania, Philadelphia, PA, USA.*

Background: Medication possession ratios (MPR) are commonly used by researchers to reflect medication exposure and adherence. MPR is the percentage of time a patient possesses a supply of a prescribed medication, which is commonly derived using pharmacy claims data. MPRs are difficult to determine with EHR prescribing (Rx) data alone due to limited ascertainment of prescription fills and no dispensing or

discontinuation data. The linkage between EHR Rx and pharmacy claims data provides a unique opportunity to study MPRs following an EHR Rx.

Objectives: The purpose was to describe the MPR for rosuvastatin in different time intervals following an EHR Rx of rosuvastatin.

Methods: We conducted a retrospective cohort study within the Optum Labs Data Warehouse, which contains de-identified administrative claims and EHR data. We included patients who had both (linked) claims (with a pharmacy benefit) and EHR data. Among patients with an ambulatory rosuvastatin EHR Rx, we determined MPRs using pharmacy claims within 1, 3, 6, and 12 months following the last rosuvastatin EHR Rx in 2012. We stratified this analysis by patients with an incident versus prevalent EHR Rx for rosuvastatin.

Results: A total of 5,486 patients had an EHR Rx for rosuvastatin, of which 60% had at least one in the prior year (prevalent cohort). Among all patients, the median MPR at 1, 3, 6, and 12 months was 90%, 66%, 63%, and 59%, respectively. The proportion of patients with an MPR ≥80% was 54%, 41%, 37%, and 34%. In the 12-month interval, MPRs increased with the number of subsequent EHR Rxs up to 82% with three EHR Rxs. MPRs were approximately 10% lower for patients with no prior rosuvastatin EHR Rx, compared to the prevalent cohort.

Conclusions: MPRs following an EHR Rx for rosuvastatin decrease for longer time intervals and for patients with an incident EHR Rx. Given the potential for exposure misclassification and poor adherence researchers using EHR data should be aware of the impact on MPRs of the length of medication exposure periods and incident versus prevalent prescribing. For exposure classification over longer time periods, researchers may consider requiring multiple EHR Rxs.

874. Patterns of Testosterone Persistence and Switching Among Commercially Insured Men in the United States

J Bradley Layton,[1] Dongmei Li,[1] Julie L Sharpless,[2] Til Stürmer,[1] M Alan Brookhart.[1] *[1]Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA [2]Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Greatly increased testosterone use during the past decade in the USA has led to increased investigation of the necessity, effectiveness, safety, and patterns of use of testosterone treatment. Expanding use among middle-aged and older men raises questions about persistence on testosterone therapy.

Objectives: To describe patterns of persistence on therapy, discontinuation, and switching of testosterone therapy within the first year of testosterone initiation in the USA.

Methods: We identified adult (18+ years), male initiators of testosterone therapy in US employer-provided commercial insurance claims or Medicare supplemental insurance in the years 2000–2012. Supplemental laboratory results were available for a subset of the sample. We required at least 1 year of continuous enrollment following initiation to observe length of initial treatment episode, switching dosage forms, and discontinuation of therapy; we also compared persistence stratified by initial dosage form, presence and result of a baseline testosterone test, year of and age at initiation, and other clinical factors to investigate differences in persistence.

Results: We identified 313,170 initiators with at least 1 year of follow-up after initiation. Seventy-eight percent discontinued testosterone treatment prior to 1 year, with 50% of initiators having 1 month's supply or less. Mean duration of initial treatment episode was 132 days (SD 121). Implant users were most likely to discontinue (92% vs. 78% overall), and patch users were most likely to switch to a different testosterone dosage form (19% vs. 7% overall). Discontinuation rates did not vary meaningfully by the presence of baseline serum testosterone testing or test results or year of initiation. However, older individuals were more likely to discontinue treatment as compared to younger initiators (ages 85+: 85%; ages 76–85: 81%; ages 66–75: 78%).

Conclusions: Persistence on testosterone therapy was low for the majority of testosterone users. The duration of treatment was brief, resulting in intermittent intervals of exposure and non-exposure within individuals.

875. Gout Control among Hypertensive Patients with Gout and the Relationship to Onset of End-Stage Renal Disease

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Sylvie Perreault,[1] Javier Nuevo,[2] Scott Baumgartner,[3] Rob Morlock.[3] *[1]Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada; [2]AstraZeneca, Madrid, Spain; [3]Ardea Biosciences, Inc, San Diego, CA, USA. [3]Ardea Biosciences, Inc, San Diego, CA, USA.*

Background: The risk of end-stage renal disease (ESRD) in both hypertension (HTN) and gout has been examined. However, the impact of allopurinol adherence as a measure of gout control on primary prevention of ESRD has not been assessed.

Objectives: Evaluate the impact of better adherence to allopurinol therapy on ESRD onset.

Methods: A cohort of 2752 patients with gout diagnosis was reconstructed using the Québec RAMQ and MED-ECHO administrative databases. Patients were eligible if they were new users of allopurinol, ages 45 to 85 years, had an HTN diagnosis and were treated with an antihypertensive drug between 1997 and 2007. A nested case–control design was used to study the occurrence of ESRD. Every case of ESRD was matched for age, sex and duration of follow-up for up to 15 controls. Adherence level was assessed as medication possession ratio. Conditional logistic regression models were used to estimate the rate ratio (RR) of ESRD adjusting for covariables.

Results: Patients had a mean age of 68 years, 82% were men, close to 50% had ≥1 cardiovascular disorder, 33% had dyslipidemia, 21% had diabetes, 15% had chronic kidney disease (stages 1 to 3), 21% were thiazides users, 33% were low-dose aspirin users and 42% were NSAID users. Clinical characteristics among patients adherent to allopurinol (1392 of 2752 overall) were similar to non-adherent patients. Major risk factor for ESRD onset was chronic kidney disease at stages 1 to 3 (RR: 8.00; CI: 3.16–22.3) and the severity of HTN (≥3 vs. <3 treatments with antihypertensives) was a trending risk factor as a crude estimate (RR: 1.94; CI: 0.68–5.51). Of 341 patients, cases ($n=22$) and controls ($n=319$), high adherence level (≥80%) to allopurinol therapy, compared with lower adherence level (<80%), was associated with a lower rate of ESRD onset (RR: 0.35; confidence interval [CI]: 0.13–0.91).

Conclusions: This population-based study suggests that better gout control may be associated with risk reduction of new-onset ESRD in the hypertensive population. Further research is needed to confirm this risk, as this study was limited by the small number of cases and potential of residual confounding factors.

876. Adherence and Persistence to Allopurinol among Hypertensive Patients with Gout

Sylvie Perreault,[1] Javier Nuevo,[2] Scott Baumgartner,[3] Rob Morlock.[3] *[1]Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada; [2]AstraZeneca, Madrid, Spain; [3]Ardea Biosciences, Inc, San Diego, CA, USA.*

Background: Medication persistence and adherence are important to treatment success, particularly where target level achievement/maintenance is critical, as in gout. Identifying barriers provides opportunity to improve patient outcomes.
Objectives: Evaluate persistence and adherence of allopurinol (ALLO) new users as well as relation to patient demographic and clinical characteristics.

Methods: We assessed profile of ALLO use among a cohort of new ALLO users after starting an antihypertensive, built using RAMQ and MED-ECHO Québec administrative databases. New ALLO users aged 45–85 years with ≥1 prescription from January 1997 to Jun 2007 were included. New users and patients with a ≥1 year gap in ALLO use ("previous ALLO users") were defined as having no ALLO prescribed in the first year prior to cohort entry. Cohort entry was defined by date of first ALLO prescription. Adherence level was estimated by medication possession ratio (MPR), cumulative persistence rates by Kaplan–Meier analysis. Cox regression models estimated rate ratio of ceasing ALLO after adjustment. Logistic regression models established relation between non-adherence level and their determinants including previous ALLO users.

Results: Of 2752 patients, mean (range) age was 70 (63–76) years, 82% men. Close to 50% had ≥1 cardiovascular disease, dyslipidemia (33%), diabetes (21%), CKD (15%), and rheumatic disease (6.3%). Patients included users of low-dose aspirin (33%) and NSAIDs (42%). During the first year, MPR was 71% and high adherence (MPR ≥80%) was 57%. Persistence decreased to 47% after 1 year follow-up (from 100% at time 0). Proportion of patients refilling ALLO during the year after cessation ranged from 67–71%. Non-persistence was more likely in patients with rheumatic disease (by 25%) and in NSAID users (by 18%). For previous ALLO users, persistence was increased by 29%. Persistence was higher for intra-articular

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corticosteroid users (by 18%) and those using ≥7 medications (by 39%). Non-adherence determinants were similar to those of non-persistence.

Conclusions: Barriers to persistence/adherence occur early during ALLO therapy. Adherence is key to determine success of many treatment approaches; greater attention may result in improved outcomes.

877. Patient and Policy-Level Determinants of Long-Acting Injectable Antipsychotic Use after Relapse: A Nationwide Study of Schizophrenia Patients in the United States

John W Jackson,[1,2,3] Lisa Fulchino,[1] James Rogers,[1] Jennifer Polinski,[1] David C Henderson,[3] Sebastian Schneeweiss,[1,2] Michael A Fischer.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Department of Medicine, Boston, MA, USA; [2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [3]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA.*

Background: Long-acting injectable antipsychotics (LAIs) were developed to reduce non-adherence in schizophrenia but are reserved as a last line therapy in the USA.

Objectives: To examine whether prescribing disparities observed for first-generation (FGA) LAIs extend to second-generation LAIs and also the impact of Medicaid prior authorization policies designed to limit drug costs.

Methods: During 2004 to 2006, a cohort of LAI-naïve Medicaid enrollees aged 18 to 64 years, diagnosed with schizophrenia and recently discharged from an inpatient or partial psychiatric hospitalization, or related emergency room visit, were drawn from Medicaid claims and followed for 90 days or until LAI initiation. We identified state-level Medicaid prior authorization policies for LAIs. Rate ratios [RR] for FGA LAI and Risperdal Consta (second generation LAI) initiation were estimated from person-month records using Poisson regression. Explained variation was sequentially compared across models including (1) adherence to oral antipsychotics, (2) demographics, (3) clinical variables, and (4) the presence of LAI prior authorization policy.

Results: Among 32 267 relapsed patients with a median adherence of 68% (proportion of non-hospital days covered), 3.1% received Risperdal Consta and 3.8% received a FGA LAI. Adherence was not associated with the use of either LAI type. Geographic and racial ethnic differences were observed for FGA LAI use. For both LAI types, longer psychiatric hospitalizations were associated with use, but duration and frequency of previous relapse episodes were not. For FGA LAI use, prior authorizations were not associated and the variation remained unexplained. For Risperdal Consta, demographics and clinical factors explained, respectively, 5.4% and 3.0% of the variation. Prior authorization policy was associated with reduced use of Risperdal Consta (RR = 0.41; 95%CI 0.20–0.87) and explained 8.4% of the variation.

Conclusions: FGA LAI prescribing appears to be driven by demographics, and prior authorization policies appear to represent a major treatment barrier for Risperdal Consta among relapsed patients. Non-adherence plays little role.

878. Persistence of Stimulants in Children and Adolescents with Attention Deficit Hyperactivity Disorder: A Longitudinal Study

Sneha Sura,[1] Satabdi Chatterjee,[1] Pravin Kamble,[2] Rajender Aparasu.[1] *[1]Pharmaceutical Health Outcomes and Policy, University of Houston, Houston, TX, USA; [2]Humana Company, Louisville, KY, USA.*

Background: Treatment persistence with stimulants is critical for long-term disease state management of attention deficit hyperactivity disorder (ADHD) in children and adolescents.

Objectives: To evaluate the persistence of long acting stimulant (LAS) use among children and adolescents with ADHD and to examine the factors associated with LAS persistence.

Methods: This retrospective longitudinal study used 2004–2007 IMS LifeLink data and included patients aged 6–19 years with ADHD diagnosis. Children continuously enrolled 6 months before and 12 months after the index date were included in the cohort. The index date was defined as the first claim date for LAS prescription. Patients were considered concurrent users if they used short-acting stimulants (SAS) or intermediate-acting stimulants (IAS) during the follow-up. All patients were followed for 12 months to measure persistence. Persistence was defined as the time from

index date to discontinuation of LAS therapy with allowable gap of ≤30 days. Accelerated failure time (AFT) model using Weibull distribution was constructed to determine the predictors of LAS persistence.

Results: A total of 40 385 patients were diagnosed with ADHD and used LAS. Among them, 14.8% and 1.58% patients were concurrently taking SAS and IAS, respectively. The mean persistence of LAS was 154 ± 129 days. Analysis of AFT model found that patients aged 13–19 years had 35% lower persistence (survival time ratio (STR), 0.65; 95%CI, 0.63-0.66) compared to those aged 6-12 years. Concurrent SAS users had higher persistence (STR, 1.18; 95%CI, 1.14-1.22) whereas concurrent IAS users had lower persistence (STR, 0.62; 95%CI, 0.57–0.68) compared to LAS users. Comorbidities such as depression, oppositional disruptive disorder and conduct disorder, and use of medications such as non-stimulants, agonists, antidepressants, antipsychotics, and mood stabilizers were also associated with longer LAS persistence.

Conclusions: The study identified several predictors of LAS persistence among children and adolescents with ADHD. There is a strong need to target factors that influence treatment persistence for long-term disease management of ADHD.

879. Utilization and Adherence Pattern of Generic and Brand-Name Drugs in the Treatment of Epilepsy

Chao Chen,[1] Ramon E Bautista,[2] Abraham G Hartzema.[1] *[1]Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA; [2]Department of Neurology, University of Florida Health Sciences Center, Jacksonville, FL, USA.*

Background: Generic drugs have the same active ingredients, dosage form and quality as their brand-name counterparts. However, surveys show patients and physicians tend to have negative perceptions of generic antiepileptic drugs (AEDs). Some researchers propose that drug use patterns and non-adherence could be one of the factors contributing to the differences in effectiveness between generic and brand-name drugs.

Objectives: This study sought to compare the utilization and adherence pattern between generic and brand-name AEDs.

Methods: Retrospective analysis was conducted using the Truven Health MarketScan® Commercial Claims and Encounters Database from 2008 to 2013. Fee-for-service patients greater than 18 years old with a diagnosis of epilepsy were identified from inpatient admission, inpatient service and outpatient service files. Only new users who had no AED prescription within 6 months before the index date were included. Patients were required to have at least 1 year continuous follow-up period. Proportion of days covered for each prescribed AED was measured as the primary endpoint. Secondary endpoints, including persistence, discontinuation and switching within 1 year follow-up, were calculated for the initial prescribed AED. Generalized linear mixed model was used to account for within-subject correlations for the primary endpoint. Covariates adjusted included demographics, disease and treatment characteristics, and health plan.

Results: The analysis included 10,961 patients and 178,639 AED refill records. Patients were less adherent when using generic AEDs compared to brand-name AEDs (adjusted odds ratio: 0.832; 95%CI: 0.775, 0.893). Furthermore, generic AED use was significantly associated with less persistence (adjusted odds ratio: 0.826; 95%CI: 0.748, 0.912), more discontinuation (adjusted odds ratio: 1.364; 95%CI: 1.240, 1.501) and more switching (adjusted odds ratio: 1.522; 95%CI: 1.356, 1.708).

Conclusions: Brand-name AED users were more adherent compared to generic AED users in this study. The reasons of this difference and whether this difference plays a role in clinical outcomes need to be further studied.

880. Drug Utilization and Adherence in Multiple Sclerosis Patients – A Nationwide Observational Study in Taiwan

Chih-Ho Chou,[1,2] Tzu-Chieh Lin,[1,3] Ching-lan Cheng,[1,3] Yea-Huei Kao Yang.[1,3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Division of Neurology, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan; [3]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan.*

Background: The incidence of multiple sclerosis (MS) varies by ethnicity and is lower in Asians than in Western countries. Interferons and glatiramer acetate are major medications for MS and recognized as disease-modifying therapy (DMT).

Objectives: The aims of this study were to delineate the prescribing pattern of DMT and adherence for MS patients in Asian population.

Methods: To delineate prescribing pattern of DMT, we retrieved patients diagnosed with MS to conduct a retrospective cohort study by using National Health Insurance Research Database between 2001 and 2009. The adherence of DMT was measured at 180, 360, 540 and 720 days after treatment initiation by medication possession ratio (MPR), each calculated by the total number of days of DMT supply divided by 180 days in the 2-year follow-up period. The good adherence was defined as an MPR $\geq$0.8, whereas an MPR $<$0.8 was considered as poor adherence. We performed multiple logistic regression to examine the factors affecting adherence.

Results: A total of 981 patients with the diagnosis of MS during the 2001 to 2009 were identified. Six hundreds and twenty-five patients (63.7%) of them had received at least one DMT prescriptions, and 74% of patients received treatment in tertiary medical centers. In patients ever treated, 84%, 15% and 1% of them received one, two and three classes DMT medications, respectively. The average MPR were 0.80, 0.60, 0.47 and 0.42 in the 180-, 360-, 540-, and 720-day intervals. Results of multiple logistic regression showed that patients living in the east area were associated with poor adherence (OR = 0.40 [0.22–0.75]). Age, gender, geographical regions, hospital levels and initial DMT did not significantly associated with MPR.

Conclusions: The percentage of patients receiving DMT in Taiwan is relatively high in comparison to other countries. However, the adherence declined early after initiation. Some patient support program may help to improve adherence. Further studies are needed to evaluate the impact of non-adherence of DMT.

881. Adherence to Inhaled Corticosteroids in Asthmatic Children in Dutch Primary Care

Marjolein Engelkes,[1] Hettie M Janssens,[2] Johan C de Jongste,[2] Miriam CJM Sturkenboom,[1] Katia MC Verhamme.[1] *[1]medical informatics, ErasmusMC, Rotterdam, The Netherlands; [2]Pediatrics, Division of Respiratory Medicine and Allergology, ErasmusMC Sophia Childrens Hospital, Rotterdam,The Netherlands.*

Background: Adherence to inhaled corticosteroids (ICS) is known to be suboptimal, which might result in poor asthma control. Knowledge on real life adherence and characteristics of children with suboptimal adherence offer opportunities to improve asthma treatment.

Objectives: To evaluate adherence (measured as medication possession rate=MPR) to ICS in children and to describe characteristics of children with good versus suboptimal ICS adherence.

Methods: Population-based cohort study within a Dutch primary care database (IPCI), containing the complete medical records of 176,516 children. First, a cohort of children with physician-diagnosed asthma, aged 5–18 years between 2000 and 2012, were selected. Amongst all children with ICS prescriptions during follow-up, MPR was calculated. Amongst children with $\geq$2 years of follow-up and $>$1 ICS prescription, characteristics were compared between children with good versus suboptimal adherence.(4th vs. 1st quartile MPR and $\geq$80% vs. $<$80% MPR)

Results: In the total asthma cohort (n = 14,303), 4000 children had $>$1 ICS prescription, mean MPR 64%. Children with $\geq$2 years of follow-up and $>$1 ICS prescription (n = 2397) had a mean MPR of 66%; 69% had a MPR$<$80%. Children with good adherence (Q4 = MPR$>$87%) were younger at start ICS and at start any respiratory medication, more often consulted a pediatrician and had more severe asthma exacerbations during follow-up compared to children with low adherence(Q1 = MPR$<$37%). Differences were similar when comparing characteristics of children with $\geq$80% versus $<$80% MPR.

Conclusions: In Dutch primary care, ICS adherence in children was suboptimal. Characteristics of children with good adherence were compatible with more severe asthma suggesting that adherence is driven by treatment need or intensity of medical follow-up. The association between adherence and risk of severe asthma exacerbations need to be studied in methodological sound studies to minimize confounding by asthma severity.

882. Longitudinal Inhaled Corticosteroid Adherence Using Multiple Methods to Calculate Medication Possession Ratios

Patrick C Souverein,[1] Ellen S Koster,[1] Alexandra L Dima,[2] Gene Colice.[3] *[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Amsterdam School of Communication Research ASCoR, University of Amsterdam, Amsterdam,The Netherlands; [3]AstraZeneca, Gaithersburg, USA.*

Background: Long-term adherence to inhaled corticosteroids (ICS) in asthma treatment is often low. However, many methods for computing adherence do not reflect variation in treatment pattern and present a single medication possession ratio (MPR), irrespective of whether patients discontinued treatment or not. **Objectives:** To assess longitudinal ICS adherence variation in asthma, using primary care prescription records in the UK.

Methods: A retrospective observational study was conducted using data from the Optimum Patient Care Research Database between 1987 and 2012. All patients, aged ≥6 years with a first ICS prescription and an asthma diagnosis were identified and followed for 2 years. ICS treatment episodes were computed under three permissible gap conditions (30, 90, and 182 days). MPRs were calculated within treatment episodes for different time windows (6-month, 8-month, 1-year, and 2-year intervals) using two methods (CMA4/CMA7). The difference between both methods involves handling of carry-over of ICS use into the relevant time window: in CMA4, this is ignored, while in CMA7, this is incorporated.

Results: From 27,185 patients starting ICS, 13,263 were excluded (data errors, no diagnosis, and missing dosage instructions), leaving 13,922 patients for analysis. Included patients were similar on socio-demographic and clinical data to those excluded. Mean age was 39 years and 51.3% were women. Within treatment episodes (90-day gap), ICS adherence ranged from 14.4–100% in the 2-year follow-up period (mean 88.9%). Varying the permissible gap in treatment episodes construction confirmed its relation with MPRs: smaller gaps resulted in higher adherences and vice versa. Mean adherence varied just slightly for the different time intervals, with CMA7 generrally yielding slightly lower mean adherences (range 87.0–90.2% vs. 89.0–92.4%), as well as adherences ≥80% (range 71.4–76.7% vs. 89.0–92.4%).

Conclusions: Differences in mean adherence were relatively small between CMA 4/7, although dichotomizing adherence at 80% had more impact. The findings highlight the importance of conceptually sound assessments of adherence and careful and transparent analysis choices.

883. Multi-dose Drug Dispensing as a Tool to Improve Medication Adherence: A Crossover Study

Nienke van Rein,[1,2] Kristel S de Geus,[1] Suzanne C Cannegieter,[3] Pieter H Reitsma,[1,2] Felix JM van der Meer,[1] Willem M Lijfering.[1,2,3] *[1]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, The Netherlands;. [2]Einthoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands; [3]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.*

Background: Multidose drug dispensing (MDD) is a dosing aid that provides patients with disposable bags containing all drugs intended for one dosing moment. It is believed that medication adherence increases when using MDD instead of individually dispensed drugs, but these studies are based on self-reported data, and results may be biased due to socially acceptable answers.

Objectives: To determine the effect of MDD on medication adherence with an objective outcome, in non-compliant patients on vitamin K antagonists (VKAs) and to determine whether MDD is equally effective as instructing patients.

Methods: Patients treated with VKAs are monitored on a regular basis and the time in therapeutic range (TTR) reflects the stability of treatment. TTR was used as a surrogate marker for adherence (i.e., objective outcome). Non-compliant patients were defined on the basis of a TTR < 75% 6 months prior to the start of MDD. The TTR before and after start of MDD were compared within patients to estimate changes in adherence after starting MDD. Non-compliant patients usually receive letters or are contacted by telephone by nurses from the anticoagulation clinic to improve adherence. To analyze whether such instruction works equally well as MDD, non-compliant patients who did not start MDD were matched to the MDD users to compare their TTR increase over time.

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Results: Eighty-three non-compliant patients started using MDD during VKA treatment. The TTR increased 13% (95%CI: 6% to 21%) within 1 month after starting MDD and remained stable during the next 5 months. The TTR of MDD as compared with non-MDD patients increased 10% more (95%CI: −1% to 22%) within 1 month but was similar after 6 months.

Conclusions: While MDD was associated with higher adherence within 1 month, MDD and instruction of patients are associated with equal improvement of drug adherence over a 6-month period.

884. The Impact of Adherence to Antidiabetic Medications on Glycaemic Control in Type 2 Diabetes Patients

Alison K Wright,[1] Darren M Ashcroft,[1] Martin K Rutter,[2] Richard Emsley,[3] Douglas T Steinke.[1] *[1]Centre for Pharmacoepidemiology and Drug Safety Research, Manchester Pharmacy School, University of Manchester, Manchester, UK; [2]Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; [3]Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, UK.*

Background: Patients with type 2 diabetes (T2D) are likely to experience worsening of glycaemic control over time. Sub-optimal adherence to medications can further worsen glucose control.

Objectives: To determine the extent to which adherence to first-line therapy enables patients to achieve recommended glycaemic targets (HbA1c≤48 mmol/mol) and to investigate other important patient and clinical factors related to adherence.

Methods: Incident T2D patients prescribed a first-line monotherapy were identified from the Clinical Practice Research Datalink (CPRD) between 01/01/05 and 31/12/09, followed-up to 31/12/12. Adherence was calculated from the medication possession ratio (MPR). Patients were defined as adherent if MPR≥80%. Good glycaemic control was defined as HbA1c≤48 mmol/mol. Multivariable logistic regression was implemented to assess factors associated with achieving therapeutic HbA1c goals.

Results: Adherent patients (34,181) observed greater reductions in HbA1c levels compared to non-adherent patients (7089); with a mean reduction of 0.6% ($p < 0.05$) and non-significant increase of 0.1% ($p > 0.05$), respectively. Only 23.1% of adherent patients reached the target HbA1c goal. Patients at greatest risk of failing to meet glycaemic targets were those with a baseline HbA1c>8.0% (OR 0.73; 95% CI: 0.78, 0.93) and BMI≥25 kg/m2 (OR 0.85; 95% CI: 078, 0.93). The odds of achieving glycaemic control increased by 4% (OR 1.04; 95%CI: 1.02, 1.06) for each additional consultation the patient attended and 26% for one or more co-morbidities (OR 1.26; 95% CI: 1.20, 1.34). Adherence was not significantly associated with achieving the target (OR 1.08; 95%CI: 0.99, 1.10). Varying the MPR threshold (four levels), the 95% MPR resulted in a non-significant opposite effect of adherence on glycaemic control; OR 0.97 (95% CI: 0.92, 1.04).

Conclusions: There may be a ceiling for optimal adherence in terms of the ability of first-line treatments to affect HbA1c, and other factors may play an important role in managing blood glucose through a multifaceted approach including, intensifying antidiabetic medication regimens earlier and more frequent physician consultations.

885. Improving Adherence Measurement for Applied Pharmacoepidemiology: Estimating the Association between Endocrine Therapy Adherence and Mortality among Women with Breast Cancer

Aaron N Winn,[1] Stacie B Dusetzina.[2] *[1]Department of Health Policy and Management, University of North Carolina, Chapel Hill, Chapel Hill, NC, USA; [2]School of Pharmacy, University of North Carolina, Chapel Hill, Chapel Hill, NC, USA.*

Background: Studies examining endocrine therapy (ET) adherence and breast cancer-related outcomes have traditionally defined adherence using the proportion of days covered (PDC). While reducing medication use to a single summary metric is appealing due to simplicity, it fails to capture heterogeneous patterns of medication use, potentially masking true treatment-outcome associations.

Objectives: We used group-based trajectory models to examine the association between ET use and breast cancer recurrence and mortality. We compare outcomes estimated using adherence trajectories with

those estimated using a standard PDC cut-point of 80%.

Methods: We examined ET adherence over 1 year for 6776 women with breast cancer who initiated ET between 2007 and 2009 using SEER-Medicare data. We excluded women who died/recurred in the 12 months after ET initiation. We used monthly group-based trajectory models and PDC of >80% to estimate 12-month ET adherence. We estimated the association between adherence measures and breast cancer recurrence and mortality beginning in year two post-initiation using adjusted Cox proportional hazard models.

Results: Trajectory models identified four adherence groups: (1) quick stops (9.0%); (2) quick decline followed by a slow increase (14.8%); (3) gradual decline (18.6%); and (4) consistently high (57.7%). Mortality was significantly associated with group assignment. The hazard rate for mortality was higher when comparing "quick stops" to "consistently high" adherers (HR = 1.67, CI = 1.095–2.510). Using a standard PDC >80% averaged over the year, there was no association between adherence and mortality. We found no association between group assignment and recurrence in any model.

Conclusions: Defining ET adherence to account for patterns of medication use via trajectory models resulted in detection of adherence-outcome associations not evident when using the standard PDC measure. Improving identification of medication use patterns may help explain how real-life adherence behaviors are associated with therapeutically driven outcomes.

886. Adherence and Persistence to Anticoagulants and Its Effect on Risk of Recurrence of Venous Thromboembolism – A Systematic Review

Pareen Vora,[1] Gunnar Brobert,[1] Kiliana Suzart-Woischnik,[1] Montse Soriano-Gabarró.[1] *[1]Global Epidemiology, Bayer Pharma AG, Berlin, Germany.*

Background: The risk of venous thromboembolism (VTE) recurrence is high in the first 6–12 months following initial VTE event, and the risk persists over time. Non-adherence and non-persistence to anticoagulants could lead to suboptimal outcomes and increased risk of VTE recurrence.

Objectives: The aim of this systematic review was to estimate 3, 6, 12 months pooled adherence and persistence to anticoagulants in patients with VTE in daily care and to estimate the risk of VTE recurrence in non-persistent and non-adherent patients.

Methods: Pubmed, Embase and CENTRAL were searched up to 03/05/2014. Studies involving VTE patients (≥18 years) treated with anticoagulants for ≥3 months and reporting persistence or adherence were included. The proportions were transformed using Freeman–Tukey double arcsine transformation and pooled using DerSimonian–Laird random effects approach. Heterogeneity was explored using sensitivity analysis, sub-group analysis, and meta-regression.

Results: Out of 15770, 15 studies (11/15 conference abstracts) were included in the review. The pooled proportion of patients persistent up to 3, 6, and 12 months of anticoagulant therapy was 78% (95% CI: 61–91%), 66% (95%CI: 46–84%) and 31% (95% CI: 23–40%), respectively. Adherence estimates could not be pooled as only two studies reported adherence of which one study reported 3 months (95.7%) and other for 12 months (23.1%). Three studies reported risk of VTE recurrence based on persistence of which one also reported risk based on adherence but the results could not be pooled. These studies showed that the risk is significantly high for non-persistent and non-adherent patients.

Conclusions: Data on real-world persistence and adherence was scarce and showed a decline with increased length of treatment. This review demonstrated that there is insufficient evidence to draw definitive conclusions. Thus, more studies are needed to examine the impact of persistence and adherence on recurrent VTE.

887. Single versus Multi-Tablet Fixed Dose Combination (FDC) HIV Treatment Regimens: A Systematic Literature Review and Meta-Analysis

Siva Narayanan,[1] Soma Nag,[1] Camelia M. Graham,[1] Patrick G. Clay.[2] *[1]Evidence Generation, Value and Access Center of Excellence, Ipsos Healthcare, Washington, DC, USA; [2]University of North Texas System College of Pharmacy, Fort Worth, TX, USA.*

Background: A comparison of all available once-daily fixed dose single tablet regimens (STR) to multi-tablet

regimens (MTR; of any frequency, containing FDC) using randomized controlled trials, observational studies, and economic models encompassing patient adherence, clinical, and economic outcomes may inform healthcare providers and policy makers involved in HIV patient management.

Objectives: Conduct systematic review and meta-analysis of published literature to compare STR to MTR.

Methods: Published literature in English between 2005 and 2014 was searched using Embase, Medline, PubMed (Medline in-process), and ClinicalTrials.gov databases. Two-level screening was undertaken by two independent researchers to finalize articles for evidence synthesis. Adherence, efficacy, safety, tolerability, healthcare resource use (HRU), and costs were assessed comparing STR to MTR. A random effects meta-analysis was performed and heterogeneity examined using meta-regression.

Results: Of the 39 articles identified for qualitative evidence synthesis, 11 had quantifiable data for meta-analysis. STR patients were statistically significantly more adherent (per respective study-defined adherence goals) compared to MTR patients of any frequency (odds ratio (OR): 2.37 (95%CI: 1.68, 3.35) ($p < 0.0001$)), twice-daily MTR (OR:2.53 (95%CI: 1.13, 5.66), and once-daily MTR (OR: 1.81 (1.15, 2.84)). Viral load suppression and changes in CD4 count at 48 weeks were comparable between groups. Severe adverse events (SAEs), grades 3–4 AEs, mortality and rate of treatment discontinuation revealed no statistically significant differences. Risk for grades 3–4 laboratory abnormalities was statistically significantly lower among STR patients (relative risk: 0.68 (95%CI: 0.49, 0.94)). Several studies reported significant reduction in HRU and costs among STR compared to MTR.

Conclusions: STR demonstrated significant impact on improving adherence, comparable efficacy, and comparable or better drug safety while lowering overall healthcare resource use and costs in comparison to MTR.

888. The Impact of Pharmacist-Led Educational Interventions on Medication Adherence and Polypharmacy in Geriatric Patients in Malaysia

Muhammad Shahid Iqbal,[1] Muhammad Zahid Iqbal,[1] Muhammad Waseem Iqbal,[2] Mohd Baidi Bahari.[1] *[1]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, AIMST University, Kedah, Malaysia; [2]Faculty of Law, University of Malaya, Kuala Lumpur, Malaysia.*

Background: Pharmacist-led educational interventions to enhance medication adherence and reduce in polypharmacy use among geriatrics patients remained unassessed in Malaysia and the Southeast Asia. Very few studies have been reported regarding medication adherence and polypharmacy among geriatric patients.

Objectives: This study was designed to evaluate the impact of pharmacist-led education interventions on how to increase medication adherence and reduce in polypharmacy among geriatrics patients.

Methods: The study was conducted on geriatric outpatients attending polyclinics and tertiary level hospital in Malaysia. Research tool and data collection forms were designed and piloted on 15 patients in a different hospital before start of the study. Data were collected by convenient sampling method, and different statistical tests were used to analyze the obtained data. Psychometric evaluation was also done by assessing acceptability, validity and responsiveness of the research tool used.

Results: A total of 220 patients were approached before and after the educational interventions, that is, 110 in each group. No significant differences were observed in either group for mean age, gender, education level and occupation whereas a significant improvement ($p < 0.001$) in knowledge about increase in medication adherence and lessen polypharmacy use were observed among study patients.

Conclusions: Educational interventions led by pharmacists can significantly reduce the use of polypharmacy and enhance medication adherence among geriatrics patients. Further studies are needed to investigate the barriers which lead to medication non-adherence and inappropriate use of polypharmacy.

889. Impact of Out-Of-Pocket Expenses on Medication Adherence in Patients Covered by Private Drug Insurance Plans

François Després,[1] Amélie Forget,[1,2] Fatima-Zohra Kettani,[1,2] Lucie Blais.[1,2,3] *[1]Faculty of Pharmacy,*

Université de Montréal, Montréal, QC, Canada; [2]Research Center, Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada; [3]Endowment Pharmaceutical Chair AstraZeneca in Respiratory Health, Montréal, QC, Canada.

Background: Higher out-of-pocket expenses have been associated with lower medication adherence in the USA, but these findings are difficult to generalize to the Canadian population due to major differences in the healthcare system.

Objectives: To evaluate the impact of out-of-pocket expenses on adherence to prescribed medications among Canadians with private drug insurance.

Methods: A retrospective cohort was constructed by selecting privately insured patients registered in the reMed database between 2008 and 20012, having medication reimbursement at the point of service, being 18–64 years old and who filled at least one prescription for a medication belonging to one of the 10 drug classes most prescribed for chronic diseases. Out-of-pocket expenses related to the medication under study at cohort entry, which included the deductible and the coinsurance, were categorized into five levels (null category and quartiles): $0, $0.01–$3.59, $3.60–$8.11, $8.12–$14.40, and $14.41–$89.99. Adherence was measured with the proportion of days covered (PDC) over 1 year for new users of the medications under study. Linear regression models were used to estimate the adjusted mean difference of the PDC between levels of out-of-pocket expenses.

Results: The cohort included 1345 patients, 43% were 35–49 years old, 26% were men, and 83% were past or non-smokers. Patients with the highest out-of-pocket expenses were found to be less adherent than those with the lowest out-of-pocket expenses (difference: –19.0%; 95%CI: –24.0 to –13.0); however, patients with no out-of-pocket expenses were less adherent than those with low out-of-pocket expenses (difference: –9.0%; 95%CI: –15.0 to –2.0).

Conclusions: Patients' adherence to prescribed medications was affected by the level of out-of-pocket expenses. Patients with no out-of-pocket expenses at the point of service might be less adherent because they place less value on their medications than do patients who must pay even a small amount.

890. Switching Antihypertensive Drug Class in Primary Healthcare: The Swedish Primary Care Cardiovascular Database (SPCCD)

Miriam Qvarnström,[1] Thomas Kahan,[1] Helle Kieler,[1] Lena Brandt,[1] Jan Hasselström,[1] Kristina Bengtsson Boström,[2] Karin Manhem,[3] Per Hjerpe,[2] Björn Wettermark.[1] *[1]Karolinska Institutet, Stockholm, Sweden; [2]R&D Centre Skaraborg Primary Care, Skövde, Sweden; [3]University of Gothenburg, Gothenburg, Sweden.*

Background: Most studies show that women have higher therapy persistence but lower class persistence than men. This study examines patterns of switching antihypertensives in women and men.

Objectives: To study sex differences among patients in a Swedish primary care population in switching after initiation of the first antihypertensive drug class.

Methods: The Swedish Primary Care Cardiovascular Database includes clinical data from medical records, socioeconomic data, dispensed drugs, and hospitalizations from national registries for 74 751 hypertensive patients in 48 primary healthcare centres. Patients (≥30 years) with diagnosed hypertension and first prescription of an antihypertensive drug between 2006 and 2007 were included. Switchers were patients with a new drug class dispensed after the initial drug class supply ended.

Results: Out of the 4997 patients included (mean age 61 years), switching was more common in women and occurred in 1295 patients (14% women, 12% men, $p = 0.0009$). There were differences in the percentage of women and men who switched the initiated drug class; angiotensin-converting enzyme inhibitor (33% women, 30 % men), combination therapy (31% women, 24% men), calcium channel blockers (30% women, 23% men), diuretics (23% women, 25% men), beta-blockers (18% women, 23% men) and angiotensin receptor blockers (20% women, 18% men). One fifth had blood pressure recorded before the switch occurred and 181 (67%) of these had elevated blood pressures.

Conclusions: The present finding that women do switch more than men confirms earlier studies, and the results on sex differences related to drug class suggests that there may be differences.

891. Health Professionals' Perceptions about

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Oral Anticancer Drugs Adherence and Shared Decision Making in Belgium and the Netherlands

Mathieu Verbrugghe,[1] Lonneke Timmers,[2] Christel CLM Boons,[2] Bart FJ Van den Bemt,[3] Jacqueline G Hugtenburg,[2] Ann Van Hecke.[1] *[1]Department of Public Health – Nursing Science, Gent University, Gent, Nederland, Belgium; [2]Department of Pharmacology and Pharmacy, VU University Medical Center, Amsterdam, The Netherlands; [3]Department of Pharmacy, University Medical Centre Nijmegen, Nijmegen, The Netherlands.*

Background: Healthcare professional-related factors are known to influence adherence with oral anticancer drugs (OACD). To date, little is known about healthcare professionals' perceptions.

Objectives: The study aims to explore healthcare professionals' perceptions and beliefs towards OACD adherence, influencing factors, and physicians' shared decision making.

Methods: A cross-sectional, multi-center observational study among healthcare professionals in hemato-oncology settings in Belgium and the Netherlands was conducted. Demographics, perceptions and beliefs (BMQ-Specific) about adherence, and shared decision making in physicians (SDM-Q-Doc) were collected. The sample consisted of 254 healthcare professionals.

Results: High scores for the perceptions about adherence were found. Especially physicians thought that patients discussed adherence with them, assumed to know the level of adherence and, thought to be able to influence adherence. Necessity beliefs were significantly higher than concerns beliefs in all professions. Being a physicians or a nurse (compared to pharmacists), and higher BMQ-necessity than BMQ-concerns were associated with higher perceptions about adherence. Among physicians high scores for shared decision making were found.

Conclusions: The results of this study could contribute to the development of interventions tailored to healthcare professionals to support patients taking OACD. In future research, the association between healthcare professionals' perceptions and beliefs and patients' beliefs and adherence level could be studied.

892. "I Just Forget To Take It" – New Media For Asthma Self-Management: Assessment of Teenagers' Preferences

Ellen S Koster,[1] Daphne Philbert,[1] Tjalling W de Vries,[2] Liset van Dijk,[3] Marcel L Bouvy,[1] Patrick Souverein.

[1]UPPER, Division Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands; [2]Department of Pediatrics, Medical Centre Leeuwarden, Leeuwarden, The Netherlands; [3]Netherlands Institute for Health Services Research, Utrecht, The Netherlands.

Background: Studies measuring inhaled corticosteroid adherence frequently report adherence rates below 50%. Medication adherence rates often decline as children become teenagers. It is important to find ways to improve medication intake behavior that easily fit into adolescents' daily life.

Objectives: To assess adolescent asthmatics needs and preferences regarding medication counseling and support, with special focus on new media.

Methods: We used a qualitative study including 21 asthmatic adolescents recruited from both primary and secondary care to explore needs and preferences. Seven young adolescents (aged 12–13 years) and seven older adolescents (aged 14–16 years) participated in two moderated asynchronous online focus groups over a 1-week period. In addition, seven adolescents (aged 12–16 years) participated in a conventional focus group. Focus groups were guided by a topic list including questions on adherence in general and needs and preferences in adherence support with special focus on new media (e.g., mobile technology, social media, and health games).

Results: In all three groups, forgetting was mentioned as major reason for not using medication as prescribed. Adolescents also mentioned lack of perceived need or beneficial effects. Parents mainly play a role in reminding to take medication and collecting refills. Suggested strategies to support medication intake behavior included a smartphone application with a reminder function and easy access to online information or use of online information. Participants were positive about sharing of (online) experiences with other teenagers.

Conclusions: Forgetfulness is a major reason for non-adherence in adolescents. Furthermore, our results suggest use of peer support may be helpful in

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stimulant good medication use. Future interventions should be aimed at providing practical reminders and should be modifiable to individual preferences.

893. Use of Electronic Health Records to Evaluate Drug Safety: Example for The Incidence of Non-Melanoma Skin Cancer in Patients with Myelofibrosis

Alex Allepuz, Iulian Alecu, Andreas Brueckner, Norbert Hollaender, Katarina Sablinska.

IMS-Global Epidemiology, Novartis, Barcelona, Spain; IMS-Oncology, Novartis, Basel, Switzerland; Quantitative Safety & Epidemiology, Novartis, Basel, Switzerland; OGD-Biometrics & Data Management, Novartis, Basel, Switzerland; IMS-Global Epidemiology, Novartis, East Hanover, USA.

Background: Throughout a drug's lifecycle, safety assessment is of utmost importance. However, information specific to the target populations to contextualize the frequency of an observed adverse event is seldom available. In this context, studies based on secondary data may provide an additional piece of information.

Objectives: We present our experience in exploring the frequency of non-melanoma skin cancer (NMSC) in patients with myelofibrosis not exposed to ruxolitinib.

Methods: The US claims database, MarketScan, was used to estimate the incidence of NMSC in patients with myelofibrosis exposed to hydroxyurea but not to ruxolitinib during the period 2006 to Q1-2013. The inclusion criteria were as follows: (1) prescription of hydroxyurea (the first ever prescription defined the index date), (2) diagnosis of myelofibrosis (ICD9: 289.83, 238.76) any time before or on the index date, and (3) at least 2 years of enrollment prior to index date. Patients were followed-up until (1) the end of enrollment, (2) the initiation of ruxolitinib, or (3) the first NMSC diagnosis (ICD9: 173.0–173.9).

Results: A total of 275 ruxolitinib-naïve patients were identified, 50 of which had a previous diagnosis of NMSC. The overall NMSC incidence rate was 6.1 cases per 100 person-years (95%CI: 4.0–9.3), and 24.3 (95%CI: 13.5–43.9) and 3.3 (95%CI: 1.8–6.2) in patients with and without previous history of NMSC, respectively. When comparing this to ruxolitinib-treated patients from the COMFORT studies, the estimated rates of NMSC in ruxolitinib-treated patients were similar to those who were ruxolitinib-naive. Because of this, it was concluded that current data suggested a reasonably similar incidence of NMSC in ruxolitinib-treated patients and historical datasets, although patients should continue to be monitored.

Conclusions: Electronic health records (EHR) could be useful in evaluating safety issues in the absence of comparative data. However, aspects related to reliable identification of the target population and the event of interest, sufficient number of cases, and information on potential confounders should be considered carefully when deciding to use EHR.

894. Incidence of Multiple Sclerosis in Germany

Lasse Pachaly,[1] Edeltraut Garbe,[1] Dunya Bentama,[2] Laura Khil,[2] Klaus Berger,[2] Niklas Schmedt.[1] *[1]Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany; [2]Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany.*

Background: Due to an increasing number of available drugs for the treatment of multiple sclerosis (MS), pharmacoepidemiological studies identifying incident MS cases are of great interest.

Objectives: To compare the impact of different MS case definitions on the incidence rate (IR) of MS in Germany.

Methods: Retrospective cohort study based on claims data from 2004 to 2009 in the German Pharmacoepidemiological Research Database with calculation of the MS incidence rate (IR) in 2008 according to different case definitions. The primary case definition required two diagnoses of MS in the same or in two consecutive quarters after 48 months without a coded MS diagnosis. The second case definition additionally required MS-specific drug treatment, which for the third case definition had to be accompanied by an MRI, lumbar puncture, and evoked potential test. Based on these definitions, the age-standardized and sex-standardized IR (sIR) of MS was calculated per 100,000 person years (py) based on the German population in 2008. IRs were further stratified by age and sex. In sensitivity analyses, the effect of reducing the required MS-free time period before MS diagnosis to 36, 24, and 12 months was evaluated.

Results: The cohort comprised 4,182,314 insurants

(46.2% women, median age 44 years). The primary case definition yielded an sIR of MS of 21.9 (95% CI: 20.5–23.6) per 100,000 py, whereas the second and third case definition resulted in substantially lower estimates (9.0; 8.0–10.1 and 5.0; 4.3–5.9, respectively). The IR was more than twice as high in women compared to men (30.2; 27.8–32.7 vs. 13.5; 12.0–15.1). Stratified by age group, the highest IR was observed in the age group 30–34 years with 56.8 (46.7–68.3). Reducing the required MS-free time period from 48 to 12 months resulted in an increase of the IR by about 6 per 100,000 py.

Conclusions: The primary case definition resulted in a substantially higher IR than those reported from other countries, whereas the IR was comparable to reported IRs for the second case definition and too low for the third case definition. To not misclassify prevalent as incident cases based on claims data, a sufficiently long MS-free time period before the initial MS diagnosis should be defined.

895.Validation of Claims Algorithms for Progression to Metastatic Cancer in Patients with Breast, Non-Small Cell Lung, and Colorectal Cancer

Jason C Simeone,[1] Beth L Nordstrom,[1] Karen G Malley,[1] Kathy H Fraeman,[1] Zandra Klippel,[2] Mark Durst,[2] John H Page,[2] Hairong Xu.[2] *[1]Evidera, Lexington, MA, USA; [2]Amgen, Inc., Thousand Oaks, CA, USA.*

Background: Administrative claims databases have no data that can directly indicate cancer progression, and the accuracy and completeness of secondary tumor International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes are known to be poor.

Objectives: To identify validated claims algorithms for progression to metastatic cancer and compare them to the presence of secondary tumor diagnosis codes alone.

Methods: Adults with stage I–III breast, non-small cell lung cancer (NSCLC), or colorectal cancer (CRC) in the Geisinger Health System from 2004–2011 were selected. Evidence of progression was extracted via manual chart review as the reference standard. In addition to secondary malignancy diagnosis, diagnoses, procedures, and treatments were selected with clinician input as indicators of cancer progression. Random forests models provided variable importance scores. In addition to codes for secondary malignancy, several more complex algorithms were constructed, and performance measures were calculated.

Results: Among women with breast cancer (17/502 [3.4%] progressed), the performance of a secondary malignancy code was suboptimal (sensitivity: 64.7%; specificity: 86.0%; positive predictive value [PPV]: 13.9%; negative predictive value [NPV]: 98.6%); requiring malignancy at another site or initiation of immunotherapy increased PPV and specificity but decreased sensitivity. For NSCLC (61/236 [25.8%] progressed) codes for secondary malignancy alone (PPV: 47.4%; NPV: 84.8%; sensitivity: 60.7%; specificity: 76.6%) performed similarly or better than more complex algorithms. For CRC (33/276 [12.0%] progressed), secondary malignancy codes had good specificity (92.7%) and NPV (92.3%) but low sensitivity (42.4%) and PPV (43.8%); an algorithm with change in chemotherapy increased sensitivity but decreased other metrics.

Conclusions: Selected algorithms performed similarly to the presence of a secondary tumor diagnosis code, with low sensitivity/PPV and higher specificity/NPV. Accurate identification of cancer progression likely requires verification through chart review.

896. On the Accuracy of Using Natural Language Processing Techniques for the Surveillance of Hospital-Acquired Pneumonia

Christian M Rochefort,[1,2,3] Aman D Verma,[1,2] Tewodros Eguale,[1,2] David L Buckeridge.[1,2] *[1]Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, QC, Canada; [2]Clinical & Health Informatics Research Groupe, McGill University, Montreal, QC, Canada; [3]Ingram School of Nursing, McGill University, Montreal, QC, Canada.*

Background: Hospital-acquired pneumonia (HAP) represents one of the most common nosocomial infections, accounting for 15% of all hospital-acquired infections and 25% of all ICU-acquired infections. HAPs are estimated to occur at a rate of between 5 and 10 cases per 1000 hospital admissions, and in 8% to 28% of the patients receiving mechanical ventilation. HAP is also associated with significant morbidity, mortality and cost. While surveillance of HAP is necessary for quality improvement, current methods are inaccurate, untimely and expensive. With the growing availability of electronic health records (EHRs) and the development of automated methods

for encoding and classifying electronic narrative documents, such as natural language processing (NLP), there is an opportunity to identify potentially better methods.

Objectives: The objective of this study was to determine the accuracy of using NLP of EHR data for performing pneumonia surveillance.

Methods: A validation study was conducted at a university health center in Montreal (Canada). We randomly sampled 4000 narrative reports of chest radiological examinations that were performed between 2008 and 2014. We manually identified pneumonia within each report, which served as our reference standard. Using a bag-of-words approach, we trained 10 alternative support vector machine (SVM) models predicting pneumonia. SVM training and testing was performed using nested 10-fold cross-validation, and the average accuracy of each model was measured and compared. We report on the accuracy of the best SVM model predicting pneumonia.

Results: On manual review, 640 (16.0%) reports were positive for pneumonia. The best SVM model predicting pneumonia achieved sensitivity of 0.83 (95%CI: 0.78–0.88), specificity of 0.98 (95%CI: 0.97–0.99), positive predictive value of 0.88 (95%CI: 0.83–0.94) and negative predictive value of 0.97 (95%CI: 0.96–0.97).

Conclusions: Statistical NLP can accurately identify pneumonia from narrative radiology reports. The SVM model validated in this study could facilitate HAP surveillance and the evaluation of preventive interventions.

897. Impact of Case Definition on Disease Incidence Rates Estimated from Administrative Claims Databases

Daina B Esposito,[1] Lina Titievsky,[2] Jennifer CL Hawes,[1] Crystal N Holick,[1] Stephan Lanes.[1] *[1]HealthCore, Inc., Andover, MA, USA; [2]Pfizer, Inc,, New York, NY, USA.*

Background: Administrative claims data are widely used for evaluation of disease incidence in large populations. Inaccuracies in underlying disease coding used in case definitions could affect estimates of incidence.

Objectives: To describe the impact of case definition on claims-based incidence estimates in a commercially insured cohort.

Methods: We identified patients aged 6–100 years with at least 1 year of continuous health plan eligibility in a large, commercially insured US population (HealthCore Integrated Research Database^{SM}, 2007–2013). We estimated background incidence rates (IR) for 36 prespecified outcomes. Because medical record review was not feasible, we used two case definitions per outcome to evaluate the impact of case definition on the estimated IR: the sensitive definition used ≥1 diagnosis in an inpatient setting or ≥2 diagnoses in an office visit setting, and the specific definition required multiple codes describing a clinician-recommended pattern of care. For each definition, the IR was calculated as the number of incident events divided by person-time at risk and presented with a 95% confidence interval (CI).

Results: Among 16,763,765 individuals, variation in IR (per 100,000 person years) by case definition depended on the outcome evaluated. For instance, the IR of thrombotic disorders was similar with the sensitive (18.27, 95%CI: 17.28–19.31) and specific (15.44, 95%CI: 14.53–16.40) definitions. For pancytopenia, however, the IR with the sensitive definition (55.54, 95%CI: 54.81–56.28) was 11-fold greater than the IR using the specific definition (4.84, 95%CI: 4.63-5.06). Demographic patterns of incidence were more consistent with the published literature when specific case definitions were used.

Conclusions: Case definitions in administrative claims data can substantially impact IR estimates. Trade-offs between sensitivity and specificity should be evaluated in the context of study objectives. Where validation by medical record review is unavailable, multiple case definitions can illustrate uncertainty of outcome ascertainment and highlight the importance of algorithm performance.

898. Getting the Right Cohort: Effect of Inclusion Criteria in Studies Using EMR and Claims

Emma Brinkley,[1] Christina Mack,[1] Tongsheng Wang,[2] Kathy Lang.[2] *[1]Real-World & Late Phase Research, Quintiles, Durham, NC, USA; [2]Value & Outcomes Advisory, Quintiles, Cambridge, MA, USA.*

Background: Claims and electronic medical records (EMR) are widely used for studying disease, treatment patterns, and effectiveness. A research challenge within these existing data is defining a representative cohort inclusive of the full target population. Changes in selection criteria in claims/EMR can result in meaningful differences in cohort size and characteristics that may affect generalizability and study results.

Objectives: In the context of a hybrid prospective study examining real-world fibromyalgia (FM) treatment patterns, we explored the effect of FM diagnosis requirements in claims and EMR data on the resulting cohort.

Methods: Within a large national EMR and claims-linked database, we created four cohorts of FM patients using different inclusion criteria with FM ICD9 diagnosis code 729.1:(C1) EMR only, (C2)1 EMR and 1 claim, (C3)1 EMR and 2+ claims and (C4)2+ claims but no EMR diagnosis. We compared cohort size, patient demographics, comorbidities, and provider characteristics.

Results: Sample sizes differed greatly with 17,263; 6715; 9846; and 23,013 patients in C1–C4, respectively, speaking to the complexity of diagnosing FM. The large size of C4 may be due to the need for multiple encounters, as reflected in claims, before confirming or ruling out diagnosis in EMR. Although demographics were similar, common FM comorbidities of fatigue, anxiety, and obesity were consistently lower in the EMR-only cohort (29%, 13%, and 10%) than in cohorts with 2+ claims (C4:40%, 21%, 13%; C3:48%, 25%, 15%). Differences in cohort size and characteristics may be due to the purpose and coverage of EMR, recorded for clinical care in a network of outpatient providers, versus claims, captures investigations of potential cases through billing in all treatment settings.

Conclusions: Careful definition of selection criteria in existing data is essential, particularly for difficult-to-diagnose conditions: claims data may capture the diagnostic process but miss confirmation/rule out of disease, while EMRs may miss those without firm clinical diagnosis. Linkage of datasets enables capture of the target population, and subsequent sensitivity analyses are needed to examine the effect of patient selection on results.

899. Validity of Cancer Diagnoses in General Practitioner Medical Records

Joan Fortuny,[1] James A Kaye,[2] Andrea V Margulis,[1] Estel Plana,[3] Brian Calingaert,[4] Susana Perez-Gutthann,[1] Alejandro Arana.[1] *[1]Epidemiology, RTI Health Solutions, Barcelona, Spain; [2]Epidemiology, RTI Health Solutions, Waltham, MA, USA; [3]Biostatistics, RTI Health Solutions, Barcelona, Spain; [4]Epidemiology, RTI Health Solutions, Research Triangle Park, NC, USA.*

Background: In a cohort study in users of antimuscarinic drugs for overactive bladder (OAB), we investigated the validity of cancer (CA) diagnoses in general practitioner (GP) medical records and the value added by other databases linkable to the Clinical Practice Research Datalink.

Objectives: To evaluate a process for identifying and verifying cases of common CAs diagnosed in 2004–2012.

Methods: Of 50,843 new users of OAB drugs without a history of CA, provisional CA cases were identified by electronic search for diagnostic codes in GP medical records. Patient profiles were reviewed and discussed by physician epidemiologists. Confirmed (CONF) cases had evidence of CA treatment, repeated use of a CA diagnostic code, or a subsequent "cancer care review" code. Non-cases in practices linkable to CA registry (CR) and hospital episode statistics (HES) data could become confirmed cases by using the linked data.

Results: The electronic search identified 1486 provisional cases in GP records, 825 from linked [LP] and 661 from non-linked [NLP] practices. Manual review of GP records confirmed 792 (96%) cases in LP and 616 (93%) in NLP. In LP, 1077 cases were confirmed, of which, 305 (28%) was not identifiable through GP records and were obtained by linkage to CR and HES data (54 from CR, 122 from HES, and 129 from both), while 184 CONF cases (17%) were identifiable only through GP records. Among 732 CONF cases identified in LP during years with CR data (2004–2010), 492 (67%) were in GP records, 619 (85%) in CR, and 593 (81%) in HES; 22 (3%) were in GP records only, 54 (7%) in CR only, and 57 (8%) in HES only; 226 (31%) were in two sources, and 373 (51%) in all three. Of these 732 cases, 33% was not in GP

records, with lower values for CA treated by GPs (breast 12%; prostate 21%) and higher values for others (lung 54%; pancreatic 55%; renal 66%).

Conclusions: The majority of CAs in GP records (similar for LP and NLP) are confirmed by profile review or other data sources. A substantial proportion of CAs in LP would be missed without CR and HES data (and are likely missed in NLP). The effect of incomplete identification of CA cases on relative risk estimates in safety studies will need to be assessed further.

900. Development of a Risk Model for Drug-Associated Inpatient Falls

Yoonyoung Choi,[1] Benjamin Staley,[2] Carl Henriksen,[1] Paul Kubilis,[1] Gigi Lipori,[2] Babette Brumback,[3] Almut G Winterstein.[1,4] *[1]Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA; [2]University of Florida Health Shands Hospital, Gainesville, FL, USA; [3]Biostatistics, College of Public Health and Health Professionals and College of Medicine, Gainesville, FL, USA; [4]Department of Epidemiology and Biostatistics, College of Public Health and Health Professionals and College of Medicine, University of Florida, Gainesville, FL, USA.*

Background: Each year, approximately 1,000,000 people in the USA fall in hospitals. Even though many falls are deemed preventable and some general risk scores for fall prevention are available, research on prediction models specific to populations on fall-risk inducing drugs (FRID) and involving real-time clinical data is limited.

Objectives: This study aimed to identify a set of risk factors associated with falls and construct a dynamic risk model specific to hospitalized patients who receive FRIDs, for real-time use in inpatient electronic health records (EHR).

Methods: We established a retrospective cohort from the two largest University of Florida (UF)-affiliated hospitals including all admissions aged ≥18 years and exposed to ≥1 FRID between January 2012 and October 2013. We identified risk factors from published literature, the national guideline clearing house and drug monographs, and operationalized each allowing for automated retrieval from electronic health records (EHR). For each of the first five hospital days, we used multivariate logistic regression to develop risk models predicting falls at the following hospital day.

Results: A total of 462 falls (0.21%) occurred in at-risk days during the study period. After univariate analyses, the initial set of 44 risk factors was reduced to 22 variables for multivariate analysis. C-statistics varied between 0.72 for hospital day 4 and 0.77 for hospital day 3, and 0.74 for a model combining all 5 days. Strongly predictive risk factors included use of high-risk FRIDs affecting postural control (high dose odds ratio (OR) = 1.94 [95%CI 1.56–2.41] and low dose OR = 1.36 [1.00–1.81]), history of falling (OR = 1.87 [1.41–2.47]), unstable gait (OR = 1.29 [1.02–1.64]), patients' overestimation of their ability to ambulate (OR = 1.40 [1.09–1.80]), history of diagnoses associated with fall risk (OR = 1.67 [1.36–2.06]) and no records for mobility assessment (OR = 1.96 [1.41–2.73]).

Conclusions: Risk models achieved satisfactory predictive validity. All risk factors were operationalized from discrete EHR fields and allow full automation for real-time prediction of high-risk patients.

901. Detection and Validation of Ototoxicity Associated with Anticancer Platinum Drugs Using a Hospital Database

Katsuhito Hori, Ayami Kato, Junichi Kawakami. *Department of Hospital Pharmacy, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan.*

Background: Anticancer platinum drugs, including cisplatin, are indicated for gastrointestinal cancer, lung cancer, and other carcinomas. The ototoxicity is known as a common side effect; however, the occurrence of ototoxicity among anticancer platinum drugs has not been determined.

Objectives: The aim of this study was to detect the ototoxicity after chemotherapy of anticancer platinum drugs using a hospital database and to validate the strategy using medical record review.

Methods: The ototoxicities after the prescription of anticancer platinum drugs (cisplatin, carboplatin, oxaliplatin, and nedaplatin) were searched from all inpatients and outpatients in Hamamatsu University Hospital (613 beds, 1140 outpatients/day). An analytical clinical information system entitled D*D in the hospital was used. The database consists of patient background information (i.e., age and gender), records of prescriptions, injections, laboratory data, and

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diagnoses. The definitive cases of those were confirmed by medical record review. The positive predictive value (PPV) was calculated. The protocol was approved by the ethics committee of Hamamatsu University School of Medicine following the ethical guideline for epidemiological research, the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health Labor and Welfare, Japan (2013).

Results: From April 2007 to May 2014, anticancer platinum drug was prescribed in 1728 patients, of which 49 patients had a record of ototoxicity. By the medical record review, 40 of those patients were diagnosed of ototoxicity by otolaryngologist, confirmed as the definitive cases with ototoxicity after platinum drugs therapy (2.3%, 95% confidence interval: 1.7–3.1%). There is no large discrepancy of incident rates among four drugs (cisplatin: 2.7%, carboplatin: 2.3%, nedaplatin: 3.8%, and oxaliplatin: 0.6%). PPV were 94.7% in case of including record of suspected ototoxicity, 81.6% excluding suspected record.

Conclusions: The ototoxicity occurrence after platinum drugs therapy was able to be detected using a hospital database.

902. Impact of the Sharp Changes in the Use of Contraception in 2013 on the Risk of Pulmonary Embolism in France

Aurore Tricotel,[1] Cédric Collin,[1] Mahmoud Zureik.[1] *[1]Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France.*

Background: In late 2012, a national pill crisis has led French women to promptly change their behavior regarding contraception, with a significant increase in the use of first-generation and second-generation combined oral contraceptives (C1G/C2G) to the detriment of third-generation or fourth-generation products (C3G/C4G).

Objectives: To assess the impact of the sharp changes in 2013 on the rate of French women hospitalized for pulmonary embolism in France.

Methods: All non-pregnant women aged 15–49 years diagnosed with pulmonary embolism were identified from the French national hospital discharge databases from 2010 to 2013. Pulmonary embolism hospitalization rates, overall and by age group, were calculated. We compared rates in 2013 with those in 2012 and with the mean rates over the precedent 3-year period (2010–2012). Expected reduction of pulmonary embolism incidence, estimated by modeling the number of expected PE based on modifications of combined oral contraceptives exposure, was also considered.

Results: In France, in 2013 compared to 2012, pulmonary embolism hospitalization incidence rate in women of childbearing age fell by 10.6%, corresponding to a reduction of 322 hospitalizations (95%CI: [−468;−156], $p < 0.0001$). The expected pulmonary embolism reduction is consistent with the observed reduction in hospitalization incidence rate (−10.2% and −10.6%, respectively). Such a pattern was not observed neither in men aged 15–49 years nor in women aged 50–69 years.

Conclusions: Sharp change in the use of contraception methods, with a decreased use of C3G/C4G, probably played a major role in the reduction of venous thromboembolism morbidity in France.

903. Risk of Fractures in patients with diabetes mellitus type 2 – results of a database analysis in the primary care setting in Germany

Karel Kostev,[1] Birgit Ehlken,[2] Franz-Werner Dippel,[3] Wolfgang Rathmann.[4] *[1]Real World Evidence Solutions, Epidemiology & Evidence Based Medicine, IMS Health, Frankfurt, Germany; [2]Real World Evidence Solutions, Epidemiology and Safety, IMS Health, Munich, Germany; [3]Gesundheitsökonomie/Versorgungsforschung, Sanofi-Aventis Deutschland GmbH, Berlin, Germany; [4]Institute for Biometrics and Epidemiology, German Diabetes Center, University Duesseldorf, Duesseldorf, Germany.*

Background: Research has shown that diabetes mellitus is associated with an increased risk of fractures compared to the general population.

Objectives: To evaluate the 10-year incidence of fractures in subjects with diabetes mellitus type 2 (T2DM) compared to subjects without diabetes mellitus in real-life setting in Germany.

Methods: This analysis was performed as a case–control study using the primary care physician (PCP) panel of the longitudinal electronic medical records

database (IMS Disease Analyzer). Subjects were identified between January 2000 and December 2012 in the general practitioner and internist panel of the database. For 1:1 matching, the following criteria were chosen: age, gender, insurance status and point in time of the first record of T2DM diagnosis. The first fracture record after the first T2DM diagnosis was evaluated. For subjects without diabetes, the first fracture record in the corresponding time period was considered. Cox regression was used to obtain hazard ratios (HR) for the risk of fractures in subjects with T2DM versus subjects without diabetes (follow-up: maximum 10 years) adjusted for demographic and clinical parameters.

Results: In total, data from 299,104 T2MD patients and 299,104 subjects without diabetes mellitus managed were considered for the analysis. Mean age was 66 ± 12 years, 51% were male and 94% were insured by statutory health insurance. Within 10 years follow-up, a fracture was recorded in 15.4% of subjects with T2DM and in 13.1% of subjects without diabetes. The overall fracture risk was increased in subjects with T2DM compared to subjects without diabetes (HR: 1.22; CI: 1.19–1.25), especially regarding fractures of the femur HR: 1.44; CI: 1.34–1.54 and fractures of the vertebral bodies (HR: 1.26; CI: 1.18-1.35).

Conclusions: Findings from real-life setting in Germany confirm an increased fracture risk in subjects with T2DM. Further research is needed to evaluate a potential association with the underlying disease T2DM and with specific antidiabetic drugs.

904. Hormonal Therapy for Breast Cancer and Diabetes Incidence among Postmenopausal Women

Melissa L Santorelli,[1,2] Tobias Gerhard,[3,4] Kitaw Demissie.[1,2,5] *[1]Rutgers Pharmacoepidemiology Program, Rutgers University, New Brunswick, NJ, USA; [2]Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA; [3]Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Piscataway, NJ, USA; [4]Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA; [5]Cancer Prevention and Control, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA.*

Background: A prior study has reported an increased risk of diabetes among postmenopausal women taking tamoxifen. Aromatase inhibitor (AI) is now considered the first line of therapy for postmenopausal women with hormone receptor positive breast cancer and its effect on the development of new-onset diabetes has not been examined.

Objectives: To evaluate the short-term effects of hormonal therapy on diabetes incidence among postmenopausal women with breast cancer

Methods: The Surveillance, Epidemiology and End Results (SEER) – Medicare linked data and records from a 5% random sample of Medicare enrollees living in SEER areas was used. Medicare Part D contains prescription refills data. Stage I–III breast cancer patients who were 65 years of age and older in 2007 and 2008 were eligible for the study. Women who filled at least two prescriptions for AI (anastrozole, exemestane, and letrozole) by the end of 2008, and within 12 months of breast cancer diagnosis, were selected (AI women). Women without cancer were selected from the 5% random sample of Medicare beneficiaries (comparison women). Baseline was defined as the earliest hormonal therapy fill date for the AI patients and a randomly assigned date in 2007–2008 for comparison women. Inpatient and outpatient diagnoses codes prior to baseline were used in both the AI and comparison women to identify and exclude patients with preexisting diabetes. AI women were frequency matched to four comparison women by age. The development of new-onset diabetes was monitored for 24 months post-baseline in both the AI and comparison women

Results: There were 2205 breast cancer patients who used AI and 8820 subjects without breast cancer. Analysis of the Cox proportional hazards model showed that there was no association between the use of AI and the development of diabetes in the 2 years post-baseline (hazard ratio:0.99; 95% Confidence Interval: 0.84 to 1.18).

Conclusions: The findings of the present study provide evidence that postmenopausal AI users do not experience an increased risk of diabetes in the 2 years post-baseline follow-up period. Whether these findings will hold with longer follow-up of AI users deserves a closer look.

905. Does Aspirin Use in Myocardial Infarction Patients Increase the Risk of Neovascular Age-Related Macular Degeneration

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Wan-Ju Annabelle Lee,[1] Ching-Lan Cheng,[1,2] Yea-Huei Kao Yang.[1,2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng-Kung University, Tainan City, Taiwan; [2]Health Outcome Research Center, National Cheng-Kung University, Tainan City, Taiwan.*

Background: The association of aspirin use and age-related macular degeneration (AMD) was controversial for decades. In two randomized control studies, aspirin use was not related to higher AMD incidence. However, in most population-based eye studies, higher incidence rate was observed in long period use of aspirin.

Objectives: To investigate the association of aspirin use and neovascular AMD (nAMD) in myocardial infarction patients.

Methods: We conducted a nested case control study by using a patient cohort with myocardial infarction (MI), which was retrieved from Taiwan's National Health Insurance Research Database (NHIRD) during 2002 to 2007. Patients received aspirin and had nAMD occurrence were classified as the case group. A frequency matching (4 to 1) to the case group with age ±2 years old), gender and the duration of MI occurrence to nAMD occurrence was performed to determine the control group. Patients with previous diagnosis of any kind of AMD for 3 years were excluded in both groups. We defined current user (≤180 days), recent user (180 to 360 days) and past user (>360 days) according to the last prescription date of aspirin as the index date. We divided both groups into five sub-groups based on the length of aspirin use to compare the odds (≤0.5 year, 1.5 to 2.5 years, 2.5 to 3.5 years, >3.5 years). Conditional logistic regression was used to estimate the association between exposure to aspirin and a diagnosis of nAMD, adjusting for relevant confounding variables.

Results: We included 94 cases and 329 controls with male gender predominant. Compared to past users, the adjusted odds ratio (OR) was 0.703 (95%CI, 0.259–2.909) and 0.684 (0.309–1.511) for recent users and current users, respectively. The association with length of aspirin use and nAMD occurrence was positive. When compared to those who used less than half year, the adjusted OR for users 1.5 to 2.5 years, 2.5 to 3.5 years, ≥3.5 years were 0.792 (0.321–0.953), 0.609 (0.219–1.698), 1.243 (0.405–3.810), and 1.421 (0.427–4.727), respectively.

Conclusions: Longer aspirin used in MI patients should be monitored with eye problems. The risk of nAMD is higher with longer aspirin use.

906. The Incremental Impact of Cardiovascular (CV) disease on the Health-Related Quality of Life (HRQoL) of Canadians with and without Diabetes Mellitus (DM)

Shelagh M. Szabo,[1] Karissa M. Johnston,[2] Hugh D. Tildesley,[3] Adrian R. Levy.[4] *[1]Redwood Outcomes, Vancouver, BC, Canada; [2]Health Economics & Epidemiology, ICON plc, Vancouver, BC, Canada; [3]Department of Endocrinology & Metabolism, University of British Columbia, Vancouver, BC, Canada; [4]Department of Community Health & Epidemiology, Dalhousie University, Halifax, NS, Canada.*

Background: There is scant agreement among researchers about the effect of multiple health conditions on HRQoL. For example, type 2 DM and CV disease often co-exist; and while each substantially lowers HRQoL, little is known about their joint effects.

Objectives: The objective here was to compare utility decrements due to CV disease among Canadians with, and without, DM.

Methods: The population-based Canadian Community Health Survey – Healthy Aging sample ($n = 30{,}865$; age >40 years), was stratified according to self-reported DM. CV conditions included prior myocardial infarction, prior stroke, angina, and other heart disease. HRQoL status, quantified by utility values, was measured using the Health Utilities Index (HUI) Mark 3. Mean (standard deviation [SD]) utilities were estimated for the DM and comparison cohorts and utility decrements, illustrating the impact of CV disease on base health status, were calculated. Utility values were adjusted for age and sex using gamma regression.

Results: The HUI was completed by 30,106 respondents (97.5%); 4259 (14.1%) had DM. The percentage of males was slightly higher (47.5% vs. 42.3%), and the frequency of CV conditions significantly higher ($p < 0.01$), among those with DM. The mean utility among the DM cohort was 0.73 (0.30), and the presence of comorbid CV disease significantly lowered mean utility by −0.22 (stroke), −0.12 (angina), −0.09 (heart attack), and −0.08 (heart disease). While the overall mean utility of the comparison cohort was

significantly higher (0.82 [0.23]; $p < 0.001$) than the DM cohort, mean utility decrements due to CV disease were similar (within 0.03) between those with, and without, DM.

Conclusions: Determining the joint contribution of multiple illnesses on HRQoL is important, because of the growing number of older adults with multiple chronic conditions. Decrements due to CV disease were similar between Canadians with and without DM, consistent with an additive model. Changing definitions of DM, time since diagnosis, and the relative timing of DM versus CV disease may affect the magnitude of HRQoL impacts.

907. Comorbid Diagnostic Categories in Myotonic Dystrophy

Cynthia Jones, Maneesh Juneja, Anne Dilley.
Safety and Benefit-Risk Management, Biogen Idec, Cambridge, MA, USA.

Background: Comorbid illnesses among myotonic dystrophy (DM) patients are known to vary considerably from patient to patient. This spectrum has not been studied in large, nationally representative samples of DM patients, and the frequencies as compared to the general non-DM population are unknown.

Objectives: The objective of this study was to estimate the frequency of comorbid diagnoses among DM patients and the odds ratios (OR) in comparison to non-DM patients within Clinformatics™ Data Mart Multiplan from Optum™, (Eden Prairie) and to determine medications commonly used within the DM population.

Methods: DM patients were selected from the database between 1 January 2004 to 8 May 2012. DM patients were identified as those with ≥2 medical claims for DM (ICD-9 Code: 359.2, 359.21, or 359.22). Two non-DM patients were matched to every DM case based on birth year, gender, time in the database, and pharmacy benefit eligibility. Comorbid diagnoses were grouped using the Clinical Classification System.

Results: A total of 3204 DM patients were identified within the database. At least 40% of DM patients had at least one claim among the 13 most numerous comorbid diagnoses, most frequently other connective tissue disease (71.4%), diseases of the heart (69.8%), respiratory infections (68.5%), other lower respiratory disease (62.2%), and eye disorders (61.9%). DM patients were more likely to experience all of these diagnoses than non-DM patients: other connective tissue disease OR: 5.43, 95%CI: 4.85–6.07; diseases of the heart OR: 7.21, 95%CI: 6.42–8.09; respiratory infections OR: 2.11, 95%CI: 1.91–2.33; other lower respiratory disease OR: 4.21, 95%CI: 3.80–4.66; and eye disorders OR: 3.12, 95%CI: 2.83–3.45. Anti-infectives (71.6%), analgesic narcotics (50.8%), hormones and corticoids (37.5%), antiarthritics (30.8%), and antidepressants (29.4%) were the most frequently used medications.

Conclusions: The odds of the most frequent comorbid diagnoses are at least twice as high among DM patients compared to non-DM patients. This analysis demonstrates the significant breadth of comorbid diagnoses among the DM population, more frequent occurrences than those observed in the general population, and the multi-systemic nature of DM.

908. Anesthesia Exposure and Risk of Dementia and Alzheimer's Disease: A Prospective Study

Erin J.A. Bowles,[1] Eric B. Larson,[1,2] Ryan P. Pong,[3] Rod L. Walker,[1] Melissa Anderson,[1] Onchee Yu,[1] Shelly Gray,[4] Paul K. Crane,[2] Sascha Dublin.[1,5]
[1]Group Health Research Institute, Group Health Cooperative, Seattle, WA, USA; [2]Department of Medicine, University of Washington, Seattle, WA, USA; [3]Department of Anesthesiology, Virginia Mason Medical Center, Seattle, WA, USA; [4]School of Pharmacy, University of Washington, Seattle, WA, USA; [5]Department of Epidemiology, University of Washington, Seattle, WA, USA.

Background: Prior studies have demonstrated conflicting results about the association between anesthesia exposure and subsequent dementia risk. However, all prior studies were retrospective, collecting anesthesia exposure after determining dementia status, which may cause bias.

Objectives: We used prospectively collected data to evaluate the associations between anesthesia exposure and dementia or Alzheimer's disease (AD) risk.

Methods: This cohort study included community-dwelling members of the adult changes in thought cohort ($N = 3988$) who were aged 65 years or older and

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free of dementia at baseline. Participants self-reported all prior surgical procedures with general or neuraxial (spinal or epidural) anesthesia at baseline and reported new procedures every 2 years. We compared people with high-risk surgery with general anesthesia, other surgery with general anesthesia, and other surgery with neuraxial anesthesia exposures to those with no surgery and no anesthesia, adjusting models for relevant covariates. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia and AD associated with time-varying lifetime and recent (past 5 years) anesthesia exposures.

Results: At baseline, 254 (6.4%) people reported never having anesthesia; 248 (6.2%) had >1 high-risk surgery with general anesthesia, 3363 (84.3%) had >1 other surgery with general anesthesia, and 123 (3.1%) had >1 surgery with neuraxial anesthesia. High-risk surgery with general anesthesia was not associated with an increased risk of dementia (HR = 0.90, 95% CI = 0.61–1.33) or AD (HR = 1.00, 95%CI = 0.64–1.56) relative to no history of anesthesia. People with any history of other surgery with general anesthesia had a lower risk of dementia (HR = 0.66, 95% CI = 0.48–0.89) and AD (HR = 0.67, 95%CI = 0.47–0.96) than people with no history of anesthesia. Any history of other surgery with neuraxial anesthesia was associated with a reduced risk of dementia (HR = 0.51, 95%CI = 0.28–0.94) but not AD (HR = 0.65, 95%CI = 0.34–1.23). There was no association between recent anesthesia or surgery exposure and dementia or AD.

Conclusions: Anesthesia exposure does not increase risk of dementia or AD in older adults.

909. Susceptibility to Infection before Diagnosis of Primary Chronic Immune Thrombocytopenia

Charlotta Ekstrand,[1] Marie Linder,[1] Honar Cherif,[2] Helle Kieler,[1] Shahram Bahmanyar.[1] *[1]Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Hemathology, Uppsala Universitet, Uppsala, Sweden.*

Background: An important complication after diagnosis of primary chronic immune thrombocytopenia (cITP) is infections, which have mostly been connected to the immunomodulation treatment. However, infections may trigger autoimmune diseases and may be a complication of an already defect immune system.

Objectives: To investigate association of cITP with serious infections requiring inpatient or outpatient care, exclusively those diagnosed within 5 years before cITP onset.

Methods: We identified 1087 adults (≥18 years) with a diagnosis of primary cITP (ICD-10 codes D69.3 and D69.4) between 2006 and 2012 using the Swedish Patient Register. Data on infections not already listed as cause of secondary ITP were also retrieved from the register. The standardized incidence ratios (SIR; the ratio of the observed to the expected number of infections), and 95% confidence intervals (CI), were estimated as a measure of relative risk. The expected numbers of infections was calculated using the rates from the general population, divided into strata of sex, age, and year of diagnosis.

Results: cITP was associated with an increased risk of serious infections required inpatient or outpatient care within 5 years before cITP diagnosis SIR = 8.74, 95% CI (7.47–10.18) with higher risk among females SIR = 11.14, 95%CI (8.81–13.90). Analysis stratified for age groups showed highest observed SIR in those younger than 60 years. Higher magnitude SIRs observed included 87.62 (45.22–153.07) for unspecified otitis media, 83.34 (43.02–145.6) for chronic viral hepatitis, 77.08 (44.03–125.18) for Candida and 13.88 (8.7–21.02) for Cystitis. The risk was increased for several respiratory infections: 12.86 (7.49–20.59) for acute upper respiratory infections, 2.28 (1.52–3.27) for pneumonia and 2.43 (1.36–4.01) for bacterial pneumonia.

Conclusions: Patients with cITP are at increased risk of a variety of serious infections before the cITP diagnosis, with more marked risk for Candida and respiratory infections. The finding of this study and our parallel analysis on anti-infective treatments indicates that infection is not only related to the immunomodulation treatment but also to the disease itself.

910. Non-infectious Wound Complications after Mastectomy Result in Additional Surgical Procedures and Early Breast Implant Loss

Katelin B. Nickel,[1] Ida K. Fox,[1] Julie A. Margenthaler,[1] Anna E. Wallace,[2] Victoria J. Fraser,[1] Margaret A. Olsen.[1] *[1]Washington University School of Medicine, St. Louis, MO, USA; [2]HealthCore, Inc., Wilmington, DE, USA.*

Background: Non-infectious wound complications

(NIWC) following mastectomy ± breast reconstruction are not routinely tracked, and data are generally limited to single-center or surgeon reports.

Objectives: Identify NIWC (e.g., hematoma, fat necrosis, dehiscence, and implant/flap complication) in a cohort of women undergoing mastectomy ± immediate breast reconstruction (IR) and determine if NIWC incidence differs by surgery type and use of implant IR.

Methods: We developed a retrospective cohort of women 18–64 years old with ICD-9-CM or CPT-4 procedure codes for mastectomy from 2004 to 2011 using commercial claims data. NIWCs ≤180 days after surgery were detected by ICD-9-CM diagnosis codes. The incidence of NIWC after mastectomy ± IR was compared using a chi-square test.

Results: A total of 18,696 mastectomy procedures in 18,085 women were identified, with IR in 10,836 (58%) procedures. The overall NIWC rate following mastectomy ± IR was 10.8% (2023/18,696); 57% of women with NIWC required surgical wound treatment (including implant removal/exchange). The incidence of NIWC was 5.8% (456/7,860) after mastectomy only, 13.4% (1101/8217) after mastectomy + implant, 18.7% (363/1942) after mastectomy + flap, and 15.2% (103/677) after mastectomy + flap and implant ($p < 0.001$).The incidence of individual complications ranged from 0.5% for fat necrosis to 2.7% for hematoma among mastectomy only and 2.7% for fat necrosis to 5.0% for dehiscence/non-healing wound among mastectomy + IR. The percentage of NIWC that resulted in surgical wound treatment varied by procedure type: 52% (236/456) for mastectomy only, 62% for mastectomy + implant (685/1101), and 46% for mastectomy + flap (167/363). Six percent of mastectomies + immediate implant had implant removal within 60 days; 75% of these removals were due to a NIWC or surgical site infection.

Conclusions: NIWC incidence varied by type of complication and by procedure. The incidence of NIWC was twofold higher after mastectomy + IR compared with mastectomy alone. NIWC were associated with surgical wound treatment, particularly in women with IR, and with early implant loss.

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913. Incidence and Predictors for Hospitalization among Patients with Heart Failure in the Uk Using Linked Primary Care and Hospitalization Data

Ana Ruigómez,[1] Alexander Michel,[2] Mar Martín-Perez,[1] Luis-Alberto García-Rodríguez.[1] *[1]Spanish Centre for Pharmacoepidemiological Research (CEIFE), Madrid, Spain; [2]Global Epidemiology, Bayer Pharma AG, Berlin, Germany.*

Background: Hospitalization is an important event in the management and prognosis of heart failure (HF).

Objectives: To ascertain rates and predictors of HF hospitalization in a cohort of incident HF patients using primary care data linked to Hospital Episode Statistics (HES).

Methods: A cohort of incident heart failure patients between January 2000 and December 2005 from practices in The Health Improvement Network (THIN) linked to HES was ascertained. The cohort was followed from first HF diagnosis to April 2011 and new or first HF hospitalizations identified. Hazard ratios (HRs) were calculated using Cox regression. Nested case–control analysis was performed using patients with HF hospitalization during follow-up as cases and remaining HF patients as controls. Predictors of HF hospitalization were identified by calculating odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Among 3516 incident HF patients, 757 (21.5%) were hospitalized at first HF diagnosis, and 1119 (32%) had an HF hospitalization during follow-up (mean 3.6 years). Incidence rates were 17.2 and 7.1 per 100 person-years among patients who were, and who were not, hospitalized at first HF diagnosis, respectively. Among patients hospitalized during follow-up, the proportion in the first month was 17.4% for patients hospitalized at first HF diagnosis and 13.6% for patients not initially hospitalized. A twofold risk of HF-hospitalization during follow-up, consistent over time, was seen in patients hospitalized at first diagnosis compared with those not initially hospitalized; adjusted HR: 2.18, 95%CI:1.92–2.48. Major predictors of HF hospitalizations were renal failure (estimated glomerular filtration rate<60ml/min; OR: 1.52, 95%CI: 1.26–1.84), valvular heart disease (OR: 1.65, 95%CI: 1.32–2.08), hyperkalemia (OR: 1.47, 95%CI: 1.11–1.95) and diabetes (OR: 1.23, 95%CI: 1.03–1.47).

Conclusions: Risk of HF hospitalization is twofold greater for HF patients hospitalized at first diagnosis and is higher among patients with renal failure, valvular heart disease, hyperkalemia and diabetes.

914. Risk for Cardiovascular Disease in Japanese Patients with Rheumatoid Arthritis: A Large-Scale Epidemiological Study Using a Healthcare Database

Kunihiko Tanaka, Kenji Hamada, Terumi Nakayama, Akihide Atsumi, Shinichi Matsuda, Tomomi Shimura, Masatomi Nemoto. *Chugai Pharmaceutical Co. Ltd, Tokyo, Japan.*

Background: Although Western epidemiological studies have indicated that patients with rheumatoid arthritis (RA) have a higher risk for cardiovascular disease (CVD) compared with the general population, there have been few epidemiological studies to verify these findings in Japan. In this study, a Japanese healthcare database was analyzed to assess risk for CVD in Japanese patients with RA.

Objectives: To understand CVD incidence, relative risk versus osteoarthritis and the association between systemic inflammation and CVD in Japanese patients with RA.

Methods: We used Medical Data Vision database mainly composed of health insurance claim data and diagnosis procedure combination data. Patients with RA first diagnosed from April 2011 to March 2014 derived from 71 hospitals in Japan were identified with the International Classification of Diseases 10th revision (ICD-10) and history of anti-RA drug prescription. Hospitalizations for CVD including ischemic heart disease, heart failure, and stroke were identified by a combination of diagnosis (ICD-10) and diagnostic procedures. CVD incidence rate per 1000 patient-years and incidence rate ratio (IRR) for RA versus osteoarthritis were calculated. Risk factors were analyzed using univariate and multivariate Cox proportional hazard models with baseline C-reactive protein (CRP) and traditional risk factors as covariates.

Results: A total of 8658 patients with RA were identified. The incidence rate for CVD in patients with RA as 61.5 per 1000 patient-years. The age-adjusted and sex-adjusted IRR for RA versus osteoarthritis was high for total CVD (2.12; 95% confidence interval [CI]: 1.93 to 2.32), ischemic heart disease (2.16; 95%CI: 1.86 to 2.50), heart failure (2.34; 95%CI: 2.07 to 2.65), and stroke (1.68; 95%CI: 1.41 to 2.00). Risk factor analysis showed a tendency for CV risk to increase with higher baseline CRP, although the difference was not statistically significant (hazard ratio, 1.43; 95%CI, 0.99 to 2.07).

Conclusions: Our study indicates an increased risk for CVD and an association between systemic inflammation and CVD in Japanese patients with RA as well as patients in the West.

915. Demographic, Co-Morbid Conditions, and Drug Utilization of Stroke Patients in a Large Us Health Insurance Claims Database

Nicholas J Everage, Sarah Gheuens, Sandra Richman, Anne Dilley, Maneesh Juneja, Madé Wenten. *Safety and Benefits Risk-Management, Biogen Idec, Cambridge, MA, USA.*

Background: Stroke is a leading cause of disability in adults; however, there is only one therapy to treat its most common form, ischemic stroke, once it has occurred. Understanding the latest information on co-morbid conditions and drug utilization provides context for future drug development.

Objectives: To describe the demographic, co-morbid conditions and drug utilization among stroke patients in a sample of the insured US population.

Methods: Stroke patients were selected from a large US health insurance claims database from 1 January 2004 to 31 December 2012. Stroke patients were defined as those with two or more ICD-9 codes (ICD-9 Code 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434, or 436) for stroke. Two controls were selected per case and matched on year of birth, gender, time in the database, and pharmacy benefit eligibility. Co-morbidities were classified using the Clinical Classification System developed by the Agency for Health Research Quality which groups ICD-9 codes into clinical categories. Odds ratios (OR) and 95% confidence intervals comparing co-morbidities in cases and controls were calculated. Medications were grouped into drug classes using the Uniform System of Classification (USC).

Results: There were 412,890 cases of stroke, equally distributed by gender and with 89% of cases occurring in patients ages ≥46 years. Common co-morbid conditions in cases with increased odds compared to controls included diseases of the heart (88%, OR: 8.7

(95%CI: 8.6–8.8)); hypertension (86%, OR: 6.9 (95% CI: 6.76–6.93)); other nervous system disorders (78%, OR: 10.4 (95%CI: 10.26–10.49)); and other connective tissue disease (77%, OR: 3.8 (95%CI: 3.80–3.87)). More than half of patients with pharmacy benefits received analgesic narcotics, cholesterol reductase, and renin angiotensin antagonists. Very few patients (<0.5%) received alteplase infusion.

Conclusions: Stroke is a serious disease and most (ischemic) strokes are not treated with alteplase. Understanding the differences between ischemic stroke patients treated with and without alteplase merits further investigation.

916. Incidence of Depression in Patients with Diabetes in Quebec: A Population-Based Cohort Study

Carlotta Lunghi,[1] Jocelyne Moisan,[2] Jean-Pierre Grégoire,[3] Line Guénette.[4] *[1]Faculty of Pharmacy, Université Laval, Québec, QC, Canada; [2]Chair on Adherence to Treatments, Université Laval, Québec, QC, Canada; [3]Population Health and Optimal Health Practices Research Unit, CHU de Québec Research Centre, Québec, QC, Canada.*

Background: Diabetes is a common chronic condition leading to considerable health and economic burdens. Depression is the leading cause of disability worldwide. Over the last years, the literature has found an association between diabetes and the risk of depression.

Objectives: To assess the incidence of depression in a population-based cohort of new users of oral antidiabetic drugs (OADs) in Quebec, Canada, and to study factors associated with the occurrence of depression.

Methods: Administrative claims data of the public health insurance in Quebec (RAMQ) were used to identify a cohort of new OAD users free of depression and aged 18 years and above between 2000 and 2006. Patients with depression were identified using the following algorithm: (1) one inpatient or psychiatric claim with ICD-9 or ICD-10 code for depression or (2) two outpatient physician claims within 12 months or (3) one outpatient claim and a prescription for an antidepressant drug within 12 months. Patients were followed from OAD treatment initiation up to (1) depression diagnosis, (2) ineligibility to the public drug plan, (3) death, or (4) 31 December 2008, whichever came first. Incidence rate was determined using person-time analysis. Factors associated with depression were identified using multivariate Cox regression analysis.

Results: We identified 114,366 new users of OADs, of which 4808 later suffered from depression in the 2000–2008 period. The median follow up period was 4.23 years. The average age at OAD treatment initiation was 65 years. The incidence rate of depression was 9.47/1,000 person-years (10.72 for women and 8.27 for men). Independent factors associated with depression included younger or older age (under 45 and over 75 years old), being a woman, having had mental disorders other than depression in the year before OAD initiation, unemployment or low income, and a higher number of comorbidities (high number of drugs taken and practitioners visited, expressed as continuous variables).

Conclusions: Depression is a common comorbidity among patients with diabetes in Quebec. Factors associated with depression among diabetics could help practitioners better identify patients at risk.

917. Challenges of Identifying Relapses among MS Patients in a Health Plan Database

Florence T Wang,[1] Nan Liu,[1] Eva Ng,[1] Audrey Muller,[2] Daniele D'Ambrosio,[2] Ewa Lindenstrøm,[2] Cheryl Enger.[1] *[1]Epidemiology, Optum, Waltham, MA, USA; [2]Department of Global Clinical Science & Epidemiology, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland.*

Background: Pharmacoepidemiologic studies are often conducted within electronic healthcare databases, yet there are no specific diagnosis or procedural codes with which to identify relapse among patients with multiple sclerosis (MS).

Objectives: To describe an approach to identify patterns of drug use that may serve as a proxy to indicate MS relapse within a commercial health insurer's administrative database.

Methods: Adult initiators of dimethyl fumarate (DMF) who were continuously treated for 180 days were identified from a claims database of a large US healthcare insurer from March 2013 to May 2014. Through September 2014, occurrences of relapse were identified using algorithms created with MS clinicians to reflect treatment guidelines, including high-dose

corticosteroid use, adrenocorticotropic hormone (ATCH) administration, and/or hospitalization episodes.

Results: Of the 2434 patients who initiated DMF, 632 patients using DMF continuously for 6 months were included in the study. Defining relapse through a course of high dose (≥500 mg daily) oral or intravenous (IV) corticosteroid treatment for 3–10 days or 80U of ATCH for 5 days yielded an incidence of relapse of <1%. Modifying the relapse definition to include a course of high-dose oral corticosteroid treatment for up to 15 days, IV corticosteroid treatment (any dosage) for up to 15 days, or 80U of ATCH for ≥5 days yielded an incidence of relapse of 1%. Lastly, identifying relapse through a course of high-dose oral corticosteroid treatment for up to 15 days, 80U of ATCH for ≥5 days, or a hospitalization episode associated with MS yielded an incidence of 2%.

Conclusions: Identifying MS relapse through claims database whilst applying strict therapeutic guidelines remains challenging. Undercapture of treatment for relapse was possibly due to nonspecific corticosteroid dosages associated with some procedure codes. When assessing real-world clinical outcomes in MS patients in a claims database, a broader definition of relapse that includes both diagnosis and treatment codes may allow for a more complete capture of MS relapse.

918. NFL Injury Surveillance and Analytics: Improving Data Collection through Use of Electronic Health Records (EHR)

Christina D Mack, Kristina Franke, Owen McCarron, Allison Bryant, Rachel Jablonski, Michael Barboza, Nancy A Dreyer. *Real-World & Late Phase Research, Quintiles, Cambridge, MA, USA.*

Background: The US National Football League (NFL) has been conducting injury surveillance for over 30 years in an effort to promote player safety. In 2014, the NFL and Players Association launched a league-wide initiative to capture healthcare information through an EHR system, allowing for a more comprehensive understanding of injury occurrence and treatment patterns. This improvement also poses challenges in terms of consistency of data collection over time and across teams.

Objectives: Describe data collection and analytic processes required to conduct high-quality surveillance and research within an EHR including challenges and opportunities for understanding treatment utilization and effectiveness.

Methods: Reporting volume trend analysis, on-site assessment of data entry processes, provider interviews and checks for completeness were conducted to evaluate consistency of use and data quality. Multiple analytic inclusion criteria were developed to identify target populations for a broad range of questions posed by players, trainers, physicians, and owners.

Results: Research questions within the EMR include (1) surveillance efforts to consistently evaluate injury trends and impact of setting; (2) injury severity and effectiveness of treatments on ability to return to play; and (3) drug utilization. Challenges include the decentralized nature of data entry between care settings; lack of use for billing; inconsistent use of EHR for recording injuries by a wide variety of personnel; and understanding differences in treatment decisions and outcome measures based on both sport-related and clinical-relatedreasons. Solutions include improvements to technical interface to reduce data entry burden, more comprehensive capture of missed time and provision of guidance broadly and through a provider subteam.

Conclusions: The NFL EHR enables comprehensive injury and illness data collection and increases continuity of care. Efforts to standardize and simplify League-wide data collection increase data quality for clinical management and analytic purposes to achieve understanding of trends in injury occurrence, risks/benefits of treatments, and effects of modifying rules and standards.

919. Feasibility Analysis of Myopic Chroidal Neovascularization (mCNV) Recording Using the THIN Database

Zdravko P Vassilev,[1] María E Sáez,[2,3] Antonio González-Pérez,[2,3] Luis A García-Rodríguez.[2] *[1]Global Epidemiology, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA; [2]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain; [3]Andalusian Bioinformatics Research Center (CAEBi), Seville, Spain.*

Background: Choroidal neovascularisation (CNV) is a common complication of pathologic myopia (PM) and important cause of impaired vision.

Objectives: To evaluate the feasibility of an epidemiological study of myopic choroidal neovascularization (mCNV) using the THIN database.

Methods: *Source population*. The Health Improvement Network (THIN) database contains computerized information entered by primary care physicians (PCPs) in the UK. The Read classification is used to code specific diagnoses, and a drug dictionary based on the Gemscript classification is used to code drugs.

Study cohort. Individuals aged 20–89 years from 1 January 2010 to 31 December 2011 who have been enrolled with their PCP for at least 2 years and have a computerized prescription history of at least 1 year.

Case ascertainment. No specific Read code is available for mCNV, and in order to identify these cases, we used two different approaches. Method 1 composed of initial computer search of 89 related Read codes followed by manual review of medical profile with free text comments. Method 2 consisted of text string search (using two different sets of strings) and manual review of comments containing these strings.

Results: The study cohort included 2,277,640 individuals. Method 1 identified 635 subjects as potential mCNV cases. The review of their medical profiles, revealed 16 mCNV cases (2.5%) and 18 PM without evidence of neovascularization (2.8%). For method 2, the 635 individuals identified by method 1 were excluded from the study cohort. The first search based on 11 strings to capture CNV-related comments, identified 1464 patients. After a manual review of the comments for a random sample of 100 of these patients, four mCNV cases (4%) and one individual with PM without CNV (1%) were identified. The second strategy used two strings to capture specifically mCNV and identified 29 patients, out of whom 24 were classified as mCNV patients (82.8%) and five with PM without confirmed CNV (17.2%).

Conclusions: Recording of treatments or diagnoses of mCNV is limited in THIN. In order to capture as many mCNV cases as possible, a combination of code-based and string-based strategies seems necessary.

920. Contrasting Adverse Event Rates among Medicare Beneficiaries with High Cardiovascular Disease Risk Taking Statins

Paul Muntner,[1] Shia T Kent,[1] Robert S Rosenson,[2] Keri L Monda,[3] Meredith Kilgore,[1] Hong Zhao,[1] Angelika D Manthripragada.[3] *[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]Mt Sinai School of Medicine, New York, NY, USA; [3]Amgen, Inc., Thousand Oaks, CA, USA.*

Background: Current guidelines recommend pharmacologic lipid-lowering therapy for patients with a history of cardiovascular disease (CVD), diabetes or with an estimated high risk for a first CVD event. These populations are often pooled together for research studies.

Objectives: To compare incidence rates and hazard ratios for co-morbidities often considered potential adverse events (AEs) of lipid-lowering therapy among Medicare beneficiaries taking statins with (1) a history of CVD, (2) diabetes or (3) at high risk for CVD.

Methods: We conducted a retrospective cohort study using the 5% random sample of Medicare beneficiaries ≥ 65 years of age from 2006 through 2011. History of CVD and diabetes and potential AEs were defined using claims-based algorithms. Beneficiaries ≥ 65 years were considered high risk for CVD if they also had claims for hypertension or dyslipidemia. AEs included muscle events, hepatitis C, hepatic disorders, intracerebral hemorrhage, hypersensitivity, primary malignancy and diabetes.

Results: There were 105,733 beneficiaries taking statins with a history of CVD, 43,460 beneficiaries with a history of diabetes and 97,839 high-risk beneficiaries. Beneficiaries were followed for a median of 4.4 years. After multivariable adjustment and compared to beneficiaries with a history of CVD, the hazard ratios (95%CI) for AEs for those with diabetes and at high CVD risk were 0.84 (0.77–0.91) and 0.65 (0.61–0.70) for muscle events, 0.68 (0.53–0.87) and 0.57 (0.46–0.72) for hepatitis C, 0.76 (0.67–0.86) and 0.54 (0.48–0.60) for hepatic disorders, 0.75 (0.66–0.86) and 0.76 (0.68–0.84) for hypersensitivity, 0.56 (0.48–0.66) and 0.51 (0.45–0.58) for intracerebral hemorrhage, and 0.95 (0.91–0.99) and 0.91 (0.88–0.94) for primary malignancy. The hazard ratio for incident diabetes was 0.63 (95%CI 0.61–0.64) comparing the high CVD risk cohort to individuals with a history of CVD.

Conclusions: These data highlight the confounding by indication that could occur when comparing potential AEs among individuals whose indications for lipid-lowering therapy vary.

921. Suicide Incidence in Post-Menopausal Women with Breast Cancer

Alex Allepuz, Katarina Sablinska.
IMS-Global Epidemiology, Novartis, Barcelona, Spain; IMS-Global Epidemiology, Novartis, East Hanover, NJ, USA.

Background: Several studies have documented that cancer is a risk factor for suicide. However, the available information for breast cancer (BC) is primarily focused on all ages and not specifically on post-menopausal women what limits its usefulness when analyzing suicide frequency in this age group.

Objectives: The aim was to estimate suicide incidence in post-menopausal women with BC and according to women's and cancer's characteristics.

Methods: The SEER-18 database, a US cancer registry, was used. Females aged 50 years or older and with a malignant BC diagnosed in 2000 or later as the only reported malignancy were included. Information on age at diagnosis, race, extent of the disease, and follow-up time was retrieved. Patients were considered to have committed suicide if the cause of death was coded as "suicide and self-inflicted injury". Overall incidence rate (IR) of suicides per 100,000 patient-years and according to year after diagnosis and cumulative incidence (CI) based on the Kaplan–Meier estimation were calculated. Relative risks (RR) were used to analyze the association of suicide with women's and cancer's characteristics.

Results: A total of 366,583 females were recruited. Suicide IR was 6.29 (95%CI: 5.21–7.61). No association was observed with age. White women and other races showed a higher risk of suicide compared with black women (RR: 5.5, 95%CI: 1.4–22.2), and also women with regional or distant BC compared with those with local disease were at higher risk, although it was not statistically significant (RR: 1.2, 95%CI: 0.8–1.8). The 5-year after diagnosis CI was 0.36 per 1000 women (95%CI: 0.29–0.45), and suicide IR decreased from 10.5 (95%CI: 7.5–14.6) during the first year after diagnosis to 4.8 (95%CI: 2.4–9.5) during the fifth year.

Conclusions: Completed suicide incidence in women with BC is lower in the USA compared with that reported in other countries (12.4–31.2). Case ascertainment, suicide definition and a potential country effect may explain part of this difference. Attempted suicides were not available what represents a limitation when using these results to interpret observed rates.

922. The Burden of Gout in A Primary Care Canadian Population with Uncontrolled Urate Levels

Dawn M Williams,[1] Cory Cowan,[1] Alain Gendron,[1] Jason Goodfield,[2] Driss Oraichi,[2] Aren Fischer,[2] Richard Borrelli,[2] Neil Liu,[2] Alison Dziarmaga.[1] *[1]AstraZeneca Canada Inc., Mississauga, ON, Canada; [2]IMS Brogan, Mississauga, ON, Canada.*

Background: Gout is caused by hyperuricemia, leading to the deposition of monosodium urate crystals in joints. To help prevent permanent joint destruction and recurrent gout flares, guidelines recommend managing serum uric acid (SUA) levels to <6 mg/dL.

Objectives: This phase of a larger gout study was to compare gout patients with controlled versus uncontrolled SUA levels in terms of demographics, clinical characteristics, and healthcare utilization.

Methods: Data for this retrospective study were extracted from IMS Evidence 360 EMR Canada, a primary care electronic medical records database in Ontario. Adult gout patients were selected if they had $\geq$1 gout diagnosis and/or $\geq$1 gout medication claim (index date) from 1 July 2008 to 30 June 2012. Patients were stratified as controlled ($<$6.0 mg/dL) or uncontrolled ($\geq$6 mg/dL) based on mean SUA levels over the post index period. All gout patients were followed for 2 years post index date. Controlled and uncontrolled cases were compared using different statistical methods.

Results: Of the total gout cohort ($n=676$), 415 patients had $\geq$1 SUA levels during the study period; 69% (286/415) was classified as uncontrolled (mean SUA $= 7.9 \pm 1.2$ mg/dL). Uncontrolled patients were younger (mean age 59 vs. 63 years) and male (83% vs. 61%) compared to controlled patients. Chronic kidney disease increased with SUA levels and uncontrolled patients had lab test results (BMI, BP, eGFR, lipids) that were more likely to deviate from normal versus controlled patients. Both groups took urate-lowering therapies similarly. More uncontrolled patients had $\geq$1 flare(s) during the 2-year follow-up period (43% vs. 15%, $p < 0.0001$) and were more likely to use NSAIDs (55% vs. 40%, $p < 0.01$). Primary care visits were higher in the controlled gout patients;

however, uncontrolled patients had a greater number of specialist referrals.

Conclusions: In this study, uncontrolled gout patients were younger, male, more likely to experience gout flares, and use NSAIDs; while this did not generate more primary care visits, it did result in a greater number of specialist referrals.

923. Effects of Methotrexate on the Risk of Myocardial Infarction among Canadian Patients with Psoriasis and Psoriatic Arthritis

Marie-Christyne Cyr,[1] Robert Bissonnette,[2] Jean Lachaine.[1,3] *[1]PeriPharm Inc., Montreal, QC, Canada; [2]Innovaderm Research Inc, Montreal, QC, Canada; [3]Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada.*

Background: The prevalence of psoriasis is up to 3% in Canada and USA. Plaque psoriasis is a common skin disease that has a significant negative impact on quality of life. Several studies have shown that psoriasis is associated with a higher risk of myocardial infarction (MI). However, no observational study has evaluated the effect of the dose of methotrexate on the risks of MI among patients with psoriasis and psoriatic arthritis.

Objectives: The aim of this study was to compare the risk of MI between patients with psoriasis and psoriatic arthritis treated with higher and lower doses of methotrexate.

Methods: Using data from the Régie de l'Assurance Maladie du Québec (RAMQ) health administrative databases of the province of Quebec, Canada, a cohort of 5523 patients aged 20 years or more who received at least one diagnosis of psoriasis or psoriatic arthritis and at least one prescription of methotrexate between 2004 and 2013 was selected. The hazard ratio (HR) of MI comparing patients with psoriasis and psoriatic arthritis treated with higher dose of methotrexate to patients treated with lower dose of methotrexate was estimated and adjusted using a Cox proportional multivariate hazards model.

Results: Patients were 63 years on average, 44% were male and were followed on average for 3.2 years. The mean weekly dose of methotrexate used during the follow-up period was 18.2 mg (S.D. 12.6 mg). A total of 1847 patients used less than 14.6 mg of methotrexate per day and 1702 used more than 20.0 mg of methotrexate per day. The incidence rate of MI was 8.8 (95%CI: 6.7–11.5) per 1000 person-years among patients with a lower dose of methotrexate compared to 3.6 (95%CI: 2.3-5.5) among patients with a higher dose. Patients on higher doses of methotrexate were found to be 45% significantly less likely to have an MI (adjusted HR = 0.55, 95%CI: 0.32–0.95) than patients using lower doses of methotrexate, adjusting for comorbidities that increase the risk to have a MI such as diabetes, hypertension or dyslipidemia.

Conclusions: The use of higher dose of methotrexate was associated with a reduction of the risk of MI among patients with severe psoriasis.

924. Development of an Approach to Identify and Quantify Statin Intolerance Using Claims Data

Paul Muntner,[1] Shia T Kent,[1] Robert S Rosenson,[2] Keri L Monda,[3] Lei Huang,[1] Hong Zhao,[1] Jeffrey R Curtis,[1] Meredith Kilgore,[1] Angelika D Manthripragada.[3] *[1]University of Alabama at Birmingham, Birmingham, AL, USA; [2]Mt Sinai School of Medicine, New York, NY, USA; [3]Amgen, Inc., Thousand Oaks, CA, USA.*

Background: It is estimated that 5% to 10% are intolerant to statins. There are no validated algorithms or diagnostic codes specific to statin intolerance.

Objectives: To describe three approaches for identifying patients with possible statin intolerance using administrative claims data.

Methods: We conducted a retrospective cohort study of Medicare beneficiaries initiating statins between 2006 and 2011. The primary definition of statin intolerance included the composite of switching from statins to ezetimibe, down-titrating statins with ezetimibe initiation, ezetimibe monotherapy, having a rhabdomyolysis or antihyperlipidemic event claim followed by statin down-titration or discontinuation, and switching between three or more types of statins over 24 months following the initiation of statins. Additional algorithms also included patients who down-titrated statins and/or discontinued statins. Demographic characteristics and comorbid conditions were calculated for each identified group and compared to statin initiators maintaining high adherence.

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Results: Among the 151 727 Medicare beneficiaries initiating statins, 66 800 (44%) maintained high adherence to high-potency statins, and 3763 (2.4%) met the primary definition for statin intolerance. The prevalence of statin intolerance increased to 7% when those who down-titrated ($n = 6642$) and to 31% those who discontinued statins ($n = 37{,}366$) were additionally included as statin intolerant. Beneficiaries with indications of statin intolerance using the primary algorithm or the primary algorithm plus statin down-titration were more likely to have diabetes (33% and 33%) and a history of coronary heart disease (47% and 45%) compared to those with high adherence (29% for diabetes and 34% for coronary heart disease). Including those who discontinued statins as statin intolerant resulted in a cohort similar to those with high adherence to high-potency statins.

Conclusions: The algorithms developed in the current study provide an initial approach for identifying statin intolerance in claims data. However, including all people who discontinue statins appears to over-estimate the prevalence of statin intolerance compared to published estimates.

925. Usage Patterns of Paracetamol in France

Mai TT Duong,[1] Abdelilah Abouelfath,[2] Regis Lassalle,[2,3] Cecile Droz,[2,3] Nicholas Moore.[1,2,3] *[1]INSERM U657, Bordeaux, France; [2]INSERM CIC-P 0005 Pharmaco-Epidemiologie, Bordeaux, France; [3]Département de Pharmacologie, Université de Bordeaux, Bordeaux, France.*

Background: Paracetamol is available over-the-counter (OTC) in most countries and rarely appear in population databases. In France, paracetamol is covered by the health insurance system, and about 85% of all paracetamol bought in pharmacies is found in the national healthcare system database.

Objectives: This study aims to describe the usage pattern of single ingredient and combined paracetamol in France.

Methods: Drug utilization study in the 1/97 sample of the French population healthcare database during 2011–2012. Patients dispensed paracetamol in 2011 were identified and classified in two groups: single ingredient paracetamol (SP) users if all their dispensations during 1-year follow-up were of SP or combined paracetamol (CP) users if at least one of their dispensations was of CP. Dispensation patterns were described and compared to a previous similar study of nonsteroidal anti-inflammatory drugs (NSAIDs).

Results: Of the 600 000 beneficiaries in the EGB in 2011, 276 204 were SP users and 64 750 were CP users. Average age was 37.5 years(SD 25), 55% female for SP and 49.9 (SD 19), 58% female for CP. Concomitant diseases were more common in CP but remained very rare (coronary heart disease 2.3% CP, 1.6% SP; diabetes 5.3% and 3.4%; severe hypertension 3.2% and 2.2%, respectively). Over 1 year, users received on average 3.3 dispensations of SP for a median total 11 defined daily dose (DDD), and 5.4 dispensations of CP for a median total 26 DDD. 61% of SP and 30 of CP users were dispensed up to 14 DDD, and 21% and 44%, respectively, more than 30 DDD. Drugs most commonly co-dispensed were NSAIDs (22% and 29% for SP and CP), and cardiovascular drugs (15% and 20%).There was a clear age-dependence in usage, with progressively longer duration of treatment with increasing age. The SP user was close to that of OTC NSAIDs (mean age 40 years, median total 7 DDD) and CP closer to prescription strength NSAIDs (mean age 47 years, median total 23 DDD).

Conclusions: These data provide a better understanding of single ingredient and combined paracetamol user population. Because of complex usage patterns, in comparisons with NSAIDs, adjustment would probably less effective than matching, for instance, on propensity scores.

926. Comparison of Claims for Sickle Cell Disease Patients Across 3 US Health Insurance Databases

Nancy N Maserejian,[1] Li Li,[1] Maneesh Juneja,[1] William Hobbs.[1] *[1]Biogen Idec, Cambridge, MA, USA.*

Background: Hydroxyurea (HU) is the only medication currently approved for prevention of sickle cell disease (SCD) complications. Data on prevalence of HU use and SCD patient characteristics are needed to identify unmet medical needs and guide drug development. Given the difficulty conducting large prospective studies, administrative databases have been used to improve understanding of SCD patient characteristics and drug utilization patterns. However, generalizability and consistency of such data across different claims sources is unknown.

Objectives: To describe claims for HU, other medications and comorbidities in SCD patients from different US insurance claims databases.

Methods: Inpatient and outpatient claims data were obtained from two commercial insurance databases (Clinformatics™ Data Mart Multi-Plan; Truven Health MarketScan® Research) and one Medicaid database (MarketScan®) covering multiple unidentified states. SCD cases were defined as patients with 2+ diagnosis codes for SCD (282.41–42, 282.6x) occurring from 2004 onwards for commercial data or 2006 onwards for Medicaid data. To examine recent HU and narcotic medication claims, a single 12-month period in 2012 was also analyzed.

Results: The total number of SCD cases was 15,499 in Clinformatics™, 22,550 in MarketScan® commercial and 17,926 in Medicaid. Mean follow-up was 3 years in all databases. Prevalence of comorbid diagnoses and top five drug codes were similar across the commercial databases but slightly higher in Medicaid. Consistent across the commercial databases, 12% of cases had HU claims in 2012; of these, 51% (Clinformatics™) or 53% (MarketScan®) had 5+ HU claims in 2012. In Medicaid, 20% of cases had HU claims, of which 49% had 5+ HU claims in 2012. Frequency of claims for narcotic pain medications varied among the databases and was lowest in the MarketScan® commercial.

Conclusions: Claims for HU were similar across the two commercial insurance databases and slightly more common in Medicaid. While these large commercial insurance databases obtain data from different sources and geographic regions, our analysis demonstrates consistency across the databases and supports their use in characterizing SCD patients.

927. Effects of a Reimbursement Restriction of Proton Pump Inhibitors among Patients with an Increased Risk of Gastric Complications

Linda E. Flinterman, Karin Hek, Joke Korevaar, Liset van Dijk.

NIVEL Netherlands Institute for Health Services Research, Utrecht, The Netherlands.

Background: Reimbursement of proton pump inhibitors (PPIs) in the Netherlands is restricted since the first of January 2012. Instead of full reimbursement, PPIs are only reimbursed when a patient needs them for a period longer than 6 months. However, the first prescription is never reimbursed. As a conceivable consequence of this change in reimbursement, healthcare providers as well as the political arena raised the question whether patients starting with NSAID or aspirin with an increased risk of gastric complications would avoid to start PPI treatment.

Objectives: To evaluate the effects of a reimbursement restriction of PPIs for patients starting NSAID or aspirin use with an increased risk of gastric complications.

Methods: The incidence of patients new on NSAID or aspirin treatment with increased risk of gastric complications who started using PPIs was studied in a large population-based primary care database in four consecutive years (2010-2013) during which the change in reimbursement occurred. Subgroups of age and different levels of social economic status were compared over time.

Results: A temporary decrease of 10% in the use of PPIs was found during the first months after the introduction of the new rules. However, such a decline in use was also seen during the years when PPIs were completely reimbursed. The overall use of PPIs in patients who started NSAID/aspirin with high risk of gastric complications increased from 65% in 2010 to 68%, 69% and, 74% in the years 2011–2013, respectively. No differences were found for different age groups or for patients with a high or low social economic status over time.

Conclusions: Reimbursement restriction of PPIs did not decrease PPI use among patients starting with NSAIDs or aspirin with an increased risk of gastric complications.

928. The Swedish Prescribed Drug Register in the Scientific Literature 2005–2013 – A Literature Review

Mikael Hoffmann,[1] Susanna Wallerstedt,[2] Björn Wettermark.[3] *[1]The NEPI Foundation, Linköping University, Linköping, Sweden; [2]Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden.*

Background: The Swedish Prescribed Drug Register (SPDR) was expanded to include individual dispensations of prescribed drugs to all residents of Sweden

($n = 9.7$ million) on 1 July 2005. Record-linkage research is possible through the use of a national personal identification number that is used in the health care and in other population-based registers.

Objectives: To quantify and characterize the scientific output from the Swedish Prescribed Drug Register from the start in 2005 up to the end of 2013

Methods: Systematic literature searches were performed (January 2005 to December 2013) in Medline, EMBASE, and PubMed by a research librarian. A broad search strategy was used, with combinations of alternative wordings of 'drug', 'register' and 'Swedish'. We screened the publications identified in the search and included studies published within the study period (not ePub ahead of print) where SPDR had been used, regardless of language. Additional studies were identified by personal knowledge and PubMed searches on Swedish authors known by the authors to publish within the field. The studies were characterized regarding type (descriptive or analytic with drug use as either exposure or outcome) and content (record-linkage, drug group(s) and population).

Results: A total of 554 publications were identified in the literature search and an additional 65 by other strategies. Two hudred four studies fulfilled the inclusion criteria and were included in the analysis. The first publications appeared in 2007 ($n = 5$), and in 2013, 59 articles using SPDR were published.

The majority of the studies were descriptive, but the fraction of analytic studies increased during the study period. In the analytic studies, the SPDR data were mainly used as exposure. Record-linkage was increasingly used, and the conditions/drugs most often studied were within the cardiovascular field.

Conclusions: The present study illustrates an encouraging development of pharmacoepidemiological research upon the establishment of a nationwide individual-based drug register with the potential to linkage to other registers.

929. Applying the Common Data Model to Analyze Multiple Claims Databases in a Study of Lymphoma among Treated Rheumatoid Arthritis Patients

Nicole Baker,[1] Hugh Kawabata,[2] Vidya Moorthy,[3] Samy Suissa,[4] Teresa A Simon.[1] *[1]Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb Company, Hopewell, NJ, USA; [2]Center for Observational Research and Data Sciences, Bristol-Myers Squibb Company, Hopewell, NJ, USA; [3]Health Economics and Outcomes Research, Mu Sigma, Northbrook, IL, USA; [4]Center for Clinical Epidemiology, Jewish General Hospital, McGill University, Montreal, Canada.*

Background: Large healthcare claims databases are often used to conduct pharmacoepidemiology studies of marketed products, such as abatacept. Using multiple databases increases the number of patients to study but requires customizations for each database. The use of a Common Data Model (CDM) structure, which standardizes variables and terminologies across databases, minimizes the need for customization.

Objectives: Apply CDM to multiple claims databases in a pharmacoepidemiology study of lymphoma in rheumatoid arthritis (RA) patients, treated with abatacept or other biologic treatments, in order to increase the number of eligible patients.

Methods: A retrospective cohort study was conducted in the CDM versions of the MarketScan Commercial and Medicare Supplemental databases (MarketScan) and the PharMetrics database among enrollees who initiated abatacept or other RA treatments between July 2006 and June 2012. Patients without 180 days of enrollment prior to drug initiation or a claim for lymphoma during this period were excluded. Person-time was computed from 180 days after the date of drug initiation until the event of interest, end of enrollment or end of study, whichever occurred first. The minimum detectable relative risk (MDRR) with 80% power – assuming background rate of 1.1 per 1000 person-years, 1:2 ratio of abatacept initiators to other RA treatment initiators and alpha of 0.5 – was calculated.

Results: There were 10,906 patients who initiated abatacept in MarketScan (12,432 person-years) and 9630 patients in PharMetrics (13,130 person-years). MDRRs were 2.22 and 2.09 in MarketScan and PharMetrics, respectively. After pooling the databases, the MDRR fell to 1.77, although variability between databases was not considered.

Conclusions: Applying the CDM to multiple databases doubled the number of patients to be included in a study of lymphoma among patients with RA and resulted in the ability to detect a lower relative risk. Further work is needed to include additional databases, understand the amount of overlap in these databases and consider the impact of variability in results.

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930. Application of Marginal Structural Models to Unbalanced Longitudinal Health Data

edmore Chamapiwa,[1] David Reeves,[1] Darren Ashcroft,[2] Evangelos Kontopantelis,[1] David Springate.[1] *[1]Centre for Primary Care, University of Manchester, Manchester, North West, UK; [2]Manchester Pharmacy School, University of Manchester, Manchester, North West, UK.*

Background: Marginal Structural Models (MSMs), a class of structural causal models, are being increasingly used in the analysis of complex longitudinal health data because of their ability to give unbiased estimates of a time-varying treatment in the presence of time-varying confounding/mediating covariates. However, MSMs assume that observations occur at regularly separated time points for all patients, whereas in "real-life" health record data, different patients are commonly seen and measured at different and irregular time points. In addition, the frequency with which a patient is seen may well be related to their health outcomes, with patients with poorer outcomes receiving more frequent consultations. The impact of unbalanced, but more realistic, data on the performance of MSMs is unknown.

Objectives: To evaluate the performance in effect estimation of inverse probability weighted MSMs in unbalanced longitudinal data.

Methods: A simulation study was conducted to compare treatment effect estimates from inverse probability weighted MSM, unadjusted generalized estimating equation (GEE) model and adjusted GEE model. Unbalanced longitudinal data were generated by sampling the number of observations and the observation times for each individual from uniform distributions. Treatment at each observation time was sampled from a Bernoulli distribution with likelihood of getting treated dependent on the confounder level. Confounder values for each individual at simulated observation times were generated using an exponential function. Outcome values at each observation time were generated using a linear mixed effects model. The data simulation and analysis were all carried out in R.

Results: A total of 100 samples, each of 10 000 individuals, were simulated for each of 23 different effect values. Percentage ranges of 95%CI of estimates containing true effect were 84%-97% for MSMs, 92%–98% for adjusted GEE and 0% for unadjusted GEE.

Conclusions: MSMs continue to give unbiased estimates when observation times of unbalanced longitudinal data are uniformly distributed. The impact of other types of distributions of observation times on performance of MSMs is currently under investigation.

931. Assessing the Agreement of Hospitalization Estimates between Three Nationally Representative US Hospital Discharge Databases, the Nationwide Inpatient Sample (NIS), the National Hospital Discharge Survey (NHDS) and the Kid's Inpatient Database (KID)

Abigail Doucette, Elizabeth Hedgeman, Jon Fryzek. *EpidStat Institute, Ann Arbor, MI, USA.*

Background: Nationally representative hospital discharge records are frequently used in health research to establish national estimates, but the comparability of their estimates remains unclear.

Objectives: To compare mean number of hospitalizations due to rare and common conditions across three nationally representative databases: the NIS, KID, and NHDS.

Methods: Hospitalizations due to rare and common conditions were assessed for years 2003 through 2009, as available, incorporating the specified sampling weight, strata and cluster for each dataset. Hospital discharges due to respiratory syncytial virus (RSV) and congenital lung disease (CLD) in non-newborn children <1 and <5 years were estimated using all three datasets; discharges due to acute myocardial infarction (AMI) and hepatitis C virus (HCV) in adults aged 18+ years were estimated in the NIS and NHDS. Differences in mean estimates across the datasets were tested by ANOVA.

Results: Mean hospital discharges due to RSV ranged from 11.2% to 11.9% ($p=0.0007$) and from 7.9% to 8.3% ($p=0.0025$) among non-newborn children <1 and <5 years of age, respectively. Mean hospital discharges due to CLD ranged from 1.6% to 1.9% ($p=0.0003$) among children <1 and from 1.3% to 1.4% ($p=0.5083$) among children <5 years of age. In adults, mean hospital discharges due to HCV ranged from 0.3% in the NHDS to 0.4% in the NIS ($p<0.0001$), and due to AMI ranged from 2.2% in the NHDS to 2.4% in the NIS ($p<0.0001$). Mean hospital discharges during the study period were significantly different among all analyses except congenital lung disease among children <5 years of age.

Conclusions: The use of one nationally representative database may not adequately support analyses estimating hospital discharge rates. Though small, a difference of 0.2% in total hospitalizations for adults represents approximately 450,000 hospitalizations across the study period. Performing sensitivity analyses using at least one other database is preferable.

932. Standardizing Event Rates in Non-Representative Data: An Applied Example

Mitchell M Conover,[1] Suzanne Landi,[1] Michele Jonsson Funk.[1] *[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.*

Background: Event rates estimated from samples with non-representative covariate distributions (e.g. convenience samples and RCTs) may be biased. External standardization is an analysis-stage adjustment method that requires fewer assumptions than regression methods. However, its use is rare in the pharmacoepidemiology literature.

Objectives: To demonstrate the impact of external standardization on calendar year and regional event rates for acute myocardial infarction (AMI), stroke, and in-hospital death (IHD) estimated from national convenience sample of healthcare claims data.

Methods: We analyzed Marketscan healthcare claims of patients aged 18 to 79 years from 2000–2012. We identified outcomes using ICD-9 diagnosis codes (AMI, stroke) and discharge status (IHD) from inpatient claims. To estimate standardized rates and 95% confidence intervals (CI), we weighted age, sex, region and calendar year specific rates to a standard US population with employer-provided insurance (2010 Current Population Survey).

Results: Person-time (PT) in the data varied by age, year and region. The proportion of patients age >64 years was highest in 2001 (15.8% of PT) and the Midwest (11.2%) and lowest in 2012 (7.4%) and the South (6.8%). For all outcomes, standardization reduced calendar year specific rates relative to the crude, with the greatest reductions in 2001 (AMI: −22.5%, stroke: −29.6% and IHD: −31.0%) and the smallest in 2012 (AMI: −0.6%, stroke: −1.1% and IHD: −2.7%). The south had the lowest crude rate of IHD (70.6 per 100,000 person-years, 95%CI: 70.1, 71.1) and relatively low crude rates of stroke (29.1, 95% CI: 28.8, 29.4) and AMI (161.4, 95%CI: 160.6, 162.1). After standardization, the south had the highest rate of IHD (74.7, 95%CI: 74.1, 75.4) and stroke (35.6, 95%CI: 35.1, 36.2) and the second highest rate of AMI (181.1, 95%CI: 179.9, 182.2).

Conclusions: Variation in covariate distributions in non-representative data may result in biased event rates. External standardization is a flexible analytical tool that can be used to estimate valid rates in the target population despite structural limitations in the data and improve the internal and external validity of findings.

933. Leveraging Real-Time Pharmacy Data from a Managed Care Organization to Collect Patient Reported Outcomes in a Real World Setting

Suvapun Bunniran,[1] Brandon Suehs,[1] Cralen Davis,[1] Claudia Uribe,[1] Daniel Ng,[2] Thomas Yuran,[2] Maria Vassilakis,[2] Matt Zajack,[1] Hugh Lee.[3] *[1]Comprehensive Health Insights, Humana, Inc., Louisville, KY, USA; [2]HECOR, Astellas Scientific & Medical Affairs, Inc., Northbrook, IL, USA; [3]Humana Pharmacy Solutions Analytics, Humana, Inc., Louisville, KY, USA.*

Background: The value of patient-reported outcomes (PROs) is important when evaluating treatment results. PROs are often used in trials, but the use of PROs in real world evidence (RWE) generation is less common; this is an illustration of a pharma–payer collaboration designed to capture RW PROs.

Objectives: (1) Describe use of claims data to identify subjects for a longitudinal PRO survey (LPS), at therapy initiation and (2) link PRO and claims data.

Methods: ***Design:*** Real-time pharmacy (Rx) claims identified mirabegron (MR) initiators and any antimuscarinic (AM) initiators within 1 week of therapy initiation. All MR and a comparable sized random sample of AM initiators were selected weekly and recruited to an LPS (3 phone surveys). ***Setting:*** Eligible patients had one new (no Rx of the medication in the past 6 months) Rx claim for MR or AM. Weekly, patients were identified and surveyed. In 4 months, 1897 MR and 16 063 AM patients were identified. ***Exposures or interventions:*** MR or AM initiators were given a PRO survey: OAB-S at baseline, 30, and 90 days. ***Main outcome measures:*** Success in contacting patients by phone proximal to therapy

initiation and response rates in the longitudinal survey. ***Statistical analysis:*** Descriptives.

Results: All MR ($n=1897$) and a random sample of AM patients ($n=2444$) were recruited. Half were successfully contacted, 53% (MR $n=1007$); 54% (AM $n=1311$). For the LPS, response rates for MR were 19% ($n=352$), 13% ($n=239$) and 9% ($n=174$) for baseline, 30 and 90 days, respectively. Similar response rates were observedfor AM: 15% ($n=365$), 10% ($n=255$) and 8% ($n=193$). Analyses included completers of all three surveys (MR $n=174$; AM $n=193$), exceeding the target sample goal ($n=150$).

Survey and claims data were linked by a unique identifier assigned by researchers, allowing for examination of outcomes.

Conclusions: Real-time claims data can be used successfully as a tool to identify potential participants for RWE studies. This study included PROs captured at therapy initiation, lowering the likelihood of recall bias and allowing for subsequent data linkage from PROs and claims.

934. Relevant Automated Healthcare Databases to Perform Studies in Oncology: Easy to Find?

Stephan Linden, Fatemeh Asadzadeh Vostakolaei, Dorothee B Bartels, Patrice Verpillat. *Global Epidemiology, Boehringer Ingelheim, Ingelheim am Rhein, Germany.*

Background: Even if large automated healthcare databases (AHDB) are increasingly accessible, database selection has to be based on the research question(s) and available data. We explored the feasibility of studies in oncology using AHDB and more specifically in non-small cell lung cancer (NSCLC) patients as new treatment advances in this leading cause of cancer mortality imply further research.

Objectives: To describe which AHDB are most suitable for studies in the oncology field by using NSCLC as an example.

Methods: We used the non-profit B.R.I.D.G.E. TO DATA® repository to review and select AHDB containing data on cancer diagnosis from Europe, Israel and North-America. We focused first on databases with sufficient information on in-, outpatient and pharmacy data allowing for analysis of medical history, drug exposure, outcomes of interest and death. We then narrowed the selection by requiring more specific NSCLC data such as disease stage, histology and mutation status.

Results: Among the selected 33 AHDB identified first on the availability of cancer diagnoses, around 50% only had comprehensive longitudinal information on inpatient, outpatient and pharmacy treatment. Cancer stage data were available in nine databases (56% in Europe), so less than a third of all (27%). Among them, all included NSCLC patients and information on histology. However, based on the retrieved information, only five were able to distinguish between non-advanced and advanced stages, and none had information on EGFR mutation status. The final selected AHDB were mainly the ones linked to specific oncology datasets, for example, SEER/Medicare in the USA, PHARMO/Eindhoven Cancer Registry in the Netherlands, or National Patient Registry/National Quality Registry for Lung Cancer in Sweden.

Conclusions: Many AHDB include cancer diagnoses. But when considering more detailed oncology information relevant for outcome analysis, the number of relevant databases is further reduced to those linked to specific oncology datasets. This may limit the scope of possible studies for oncology research.

935. Validity of Cancer Diagnosis in UK Primary Care Databases: Comparison of Observed and Expected Cancer Incidence Rates

Michael Rañopa,[1] Ian Douglas,[1] Tjeerd van Staa,[1,2,3] Liam Smeeth,[1] Krishnan Bhaskaran.[1] *[1]Non-Communicable Disease Epidemiology, LSHTM, London, UK; [2]Institute of Population Health, University of Manchester, Manchester, UK; [3]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.*

Background: UK primary care data are frequently used in research studies with cancer outcomes, but the validity of cancer diagnosis information in such databases is unclear.

Objectives: For the four most common cancers, we aimed to compare incidence rates (IRs) calculated using Clinical Practice Research Datalink (CPRD) primary care data, with published national IRs based on cancer registrations. Secondly, we aimed to assess the impact of incorporating cancer registry data linked to CPRD when estimating IRs.

Methods: A random sample of 2 million patients was selected from the CPRD. Cases of breast, colorectal, lung, and prostate cancer were identified over the period 2000–2010 using Read codes. Two sets of age-specific and sex-specific IRs were estimated: (i) CPRD definite rates; (ii) updated CPRD rates incorporating linkage to the National Cancer Data Repository (NCDR). IRs were compared with national estimates published by the UK Office for National Statistics (ONS).

Results: Overall CPRD cancer IRs (per 100 000 person-years) were lower compared to ONS reported rates: breast (CPRD, 140.2 vs ONS, 145.2); colorectum (Male: CPRD, 52.9 vs ONS, 66.0; Female: CPRD, 41.2 vs ONS, 52.2); lung (Male: CPRD, 52.6 vs ONS, 73.8; female: CPRD, 39.7 vs ONS, 50.8); prostate (CPRD, 108.1 vs ONS, 117.8). Larger disparities were observed among the elderly, and during earlier years of the study period. Compared to ONS rates, updated IRs incorporating linked NCDR data (including all cases) were similar for colorectal and lung cancer, but higher for breast and prostate cancer: breast (159.3); colorectum (Male: 67.7; Female: 55.1); lung (Male: 71.6; Female: 53.3); prostate (135.6).

Conclusions: Consistent with previous studies, CPRD cancer IRs were lower compared to ONS IRs and the disparity varied by age and cancer type. This was no longer the case when linkage to the NCDR was incorporated, but for breast and prostate cancer, incidence rates were then higher than expected, implying that a proportion of these cancer cases in CPRD are either false-positive or not registered nationally.

936. A Study on Treatment and Characteristics of Prostate Cancer Patients Using Real-World Data

Jamilette Miranda,[1] Birgitta Lilja,[1,2] Björn Wettermark,[1,2] Gunnar Ljunggren,[1,3] Roger Henriksson.[1,4] *[1]Department of Development, Public Healthcare Services Committee Administration, Stockholm County Council, Stockholm, Sweden; [2]Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; [3]Department of Learning, Informatics, Management and Ethics, Medical Management Centre, Karolinska Institutet, Stockholm, Sweden; [4]Regional Cancer Centre Stockholm Gotland Stockholm and Department of Radiation Science, Oncology, University of Umeå, Stockholm County Council, Stockholm, Sweden.*

Background: Improved diagnosis and therapeutic opportunities may have a positive impact on the prognosis of prostate cancer, the most common cancer disease among Swedish men. Access to healthcare and socioeconomic data from multiple sources can facilitate studies evaluating interventions and outcomes in entire diseased populations.

Objectives: The main purpose of this study was to describe treatments and comorbidity among prostate cancer patients in the Stockholm-Gotland region (2.2 million inhabitants).

Methods: This cross-sectional, retrospective registry study, based on eight national and regional registries, included 3761 men diagnosed with prostate cancer during 2009–2010 and alive at the end of the period. Data on diagnosis, comorbidity, dispensed drugs, surgery, radiotherapy and socioeconomics were linked using the national personal identification number.

Results: The mean age in the population was 68 ± 9 (mean ± SD) years. Drug treatment was recorded for 1231 patients. The most common drugs received were bicalutamide (29.6%), leuprorelin (18.7%) and goserelin (4%). Prostatectomy and orchiectomy were reported for 916 and 43 patients, respectively. Curative and palliative radiotherapy were documented for 631 and 36 patients, respectively. Circulatory, urogenital and musculoskeletal diseases, the most common comorbidities, had a total prevalence of 29.5%, 28% and 16%, respectively, and were positively associated to age. At least one additional cancer disease was recorded for 125 patients during the period. Older patients and those with less than 10 years in school had more advanced primary tumors (T3–T4).

Conclusions: Information about prostate cancer patients in real-world settings was obtained on characteristics, comorbidity and drug treatment by linking individual data from different registries. One third of all patients with prostate cancer in the region received drug treatment and surgery. The distribution of circulatory, urogenital and musculoskeletal diseases was similar to that in the general population.

937. Validation of Laboratory Values in a Heterogeneous Healthcare System: The US Veterans Affairs Experience

Sanjay P Raju,[1] Yuk-Lam Ho,[1] Andrew Zimolzak,[1] Beth Katcher,[1] Valmeek Kudesia,[1] Kelly Cho,[1,3]

David R Gagnon.[1,2] *[1]Massachusetts Veterans Epidemiology Research and Information Center [MAVERIC]U.S. VA Cooperative Studies Program, Boston, MA, USA; [2]Biostatistics, Boston University School of Public Health, Boston, MA, USA; [3]Division of Aging, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA.*

Background: The US Veterans Administration (VA) consists of over 150 medical centers with an electronic health records (EHR) system with over 20 million patients over 18 years. Due to varied nomenclature and standards between the hospitals, laboratory tests are not easy to extract. To maximize the number of valid labs from the EHR we have designed a curation process that uses medical coding practices, database querying, descriptive statistics, and medical expert knowledge.

Objectives: To present the adjudication and curation of serum sodium values as an example of our adjudication and documentation system.

Methods: We used liberal text searches to find potential laboratory tests. These were stratified by test name, specimen source, and hospital ID [STA3N] to account for differing naming practices by institution. Tests with extremely low frequencies (<10) and undesired sources [e.g., urine] were removed. Percentile values (1%, 25%, 50%, 75%, and 99%) of the remaining tests were adjudicated independently by two medical experts. Maximum and minimum values were ignored as probable lab errors. Accepted labs were then merged with Logical Observation Identifiers Names and Codes (LOINC), and additional labs with acceptable LOINC codes were added to a second expert review. Results and documentation for serum sodium are presented.

Results: Initial extractions using the text string "sodium" produced 1799 unique tests representing 148,087,622 observations. Initial adjudication accepted 444 tests [141,438,671 obs]. An additional 1537 tests [13,773,095] were detected with the additional LOINC codes, mostly representing labs using the "Na" label. Final adjudication resulted in 729 tests [154,911,495 obs]. Documentation for this adjudication process will be presented.

Conclusions: A formal system for the adjudication of laboratory values in a heterogeneous EMR environment allows for studies where there is as much faith in the quality of exposure data as there is in either outcome or genetic data. A proper system of documentation allows for the sharing of data definition algorithms and avoids "reinventing the wheel" with each research project.

938. Identification of Device Attributes of Total Hip Replacements via Linkage to the Veterans Health Administration's National Prosthetic Patient Database

Katherine Etter,[1,2] Art Sedrakyan,[3] David D Dore.[4,1] *[1]Health Services, Policy & Practice, Brown University, Providence, RI, USA; [2]Center for Restorative and Regenerative Medicine, Providence VA Medical Center, Providence, RI, USA; [3]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, USA; [4]Optum, Waltham, MA, USA.*

Background: Large studies of most implantable medical devices using health insurance claims data have not been feasible due to lack of detailed device information.

Objectives: To identify femoral head size and bearing surface material of total hip replacement devices among a cohort of veterans identified from the Veterans Health Administration's (VHA) administrative records via the National Prosthetic Patient Database (NPPD).

Methods: Veterans with a total hip replacement surgery between 2002 and 2011 identified within the VHA's corporate data warehouse were matched to an NPPD order with 30 days of surgery. We located model numbers and references to device attributes from fields within NPPD. When model numbers were missing from the model number field, we applied SAS Perl Regular Expressions to locate numeric sequences that matched known patterns of model numbers in free text fields. Using the manufacturer's name and the model number from device catalogs, we assigned the femoral head size and material type to each order.

Results: Of the 24,874 surgeries, we matched both femoral head size and bearing surface for 9724 (39%). The age distribution of all surgeries (<40 1%, 40–49 7%, 50–59 30%, 60–69 37%, and 70+ 25%) versus matched surgeries (<40 1%, 40–49 8%, 50–59 30%, 60–69 35%, and 70+ 28%) were similar. Partial information (either the femoral head or acetabular cup) was available for an additional 3226 surgeries (13%). The model number field was missing in 89% of orders. It is likely that additional model information was present; however. we were unable to capture due to the limitations of Regular Expressions.

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Conclusions: It is feasible to create a virtual device registry by linking the NPPD to the corporate data warehouse. These data are readily available at the VA. Identification of specific device attributes was feasible in less than one-half of instances, but it appears that more sophisticated processing of free text would improve the identification of device attributes. The NPPD holds promise in offering device information on a range of surgical implants.

939. Opportunities and Challenges of Using Real World Data in Oncology: Demonstrations of Truven Marketscan and IMS Oncology Electronic Medical Records Databases

Lei Chen,[1] Cinira Lefèvre,[2] James A Michael,[1] Dale Quentin Marmaduke,[1] Jonathan Lucas Swain,[1] Lucy Mitchell,[3] Yu Yan.[1] *[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Former Eli Lilly Employee, Rueil-Malmaison, France; [3]Eli Lilly and Company, Erl Wood, UK.*

Background: Evidence from oncology clinical trials does not always translate into decision making in practice. Real world data (RWD) has been increasingly used to supplement oncology clinical trial data. However, a comprehensive understanding of opportunities and challenges of various oncology RWD in the USA is currently inadequate.

Objectives: To evaluate the strengths and limitations of two databases in the USA covering two different data sources in oncology research: Truven MarketScan Research Data (US claims data) and IMS Oncology EMR (US oncology EMR).

Methods: To identify cancer patients from Truven in 2008–2012 and IMS Oncology EMR in 2000–2012 and characterize demographics, pre-cancer data availability, major tumor types, and other characteristics of the two cohorts.

Results: Truven had more cancer patients ($N = 3{,}114{,}120$) than IMS Oncology EMR ($N = 713{,}617$). Cancer patients ≥65 years were more represented in IMS Oncology EMR (43.3%) than in Truven (37.1%). Truven cohort had longer medical history available (median 384 days) than IMS Oncology EMR (54 days). Cancers of breast, prostate, and colorectal were the most prevalent tumor types in Truven; and breast, lung and colorectal cancers were most prevalent in IMS Oncology EMR. Further, IMS Oncology EMR contained EMR specific information (e.g., race, weight, height, stage, histology, and line of therapy) that was not readily available in Truven.

Conclusions: Of the two databases, Truven covered a larger cancer cohort with a comprehensive capture of treatment data; thus, it is a good source for pharmacoepidemiology; however, the less represented elderly and lack of tumor-specific data warrant consideration when this information is essential. Detailed tumor and other information specific to IMS Oncology EMR present its unique value in oncology research, especially for specific tumor types. Given the key similarities and differences across various data sources, it is important for researchers to understand the opportunities and challenges each database brings and make informed decisions on how to leverage RWD to better support cancer patient benefit-risk profile in practice.

940. Identifying Cases of Type 2 Diabetes from Heterogeneous Data Sources: Strategy from the EMIF Project

Giuseppe Roberto,[1] Ingrid Leal,[2] Naveed Sattar,[3] Katrina Loomis,[4] Paul Avillach,[2] Peter Egger,[5] Rients van Wijngaarden,[6] David Ansell,[7] Sulev Reisberg,[8] Alessandro Pasqua,[9] Lars Pedersen,[10] James Cunningham,[11] Lara Tramontan,[12] Miguel Angel Mayer,[13] Ron Herings,[6] Preciosa Coloma,[2] Francesco Lapi,[1] Miriam Sturkenboom,[2] Johan van der Lei,[2] Martijn Schuemie,[14, 15] Peter Rijnbeek,[2] Rosa Gini.[1] *[1]Agenzia Regionale di Sanità della Toscana, Osservatorio di Epidemiologia, Florence, Italy; [2]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands; [3]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [4]Pfizer Worldwide Research and Development, Groton, CT, USA; [5]GlaxoSmithKline, Worldwide Epidemiology GSK, Stockley Park West, Uxbridge, UK; [6]PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands; [7]The Health Improvement Network, Cegedim Strategic Data Medical Research Ltd, London, UK; [8]Quretec, Software Technology and Applications Competence Center, University of Tartu, Tartu, Estonia; [9]Health Search, Italian College of General Practitioners and Primary Care, Florence, Italy; [10]Department of Clinical Epidemiology, Aarhus University Hosptial, Aarhus, Denmark; [11]University of Manchester, Manchester, UK; [12]Arsenàl.IT Consortium, Veneto's Research Centre for e-Health Innovation, Treviso, Italy; [13]Research Programme on*

Biomedical Informatics (GRIB), IMIM - Universitat Pompeu Fabra, Barcelona, Spain; [14]Janssen Research & Development, Epidemiology, Titusville, NJ, USA; [15]Observational Health Data Sciences and Informatics, New York, NY, USA.

Background: The European Medical Information Framework (EMIF) project is developing an infrastructure to combine existing healthcare data to perform observational (pharmaco)epidemiological studies involving a wide variety of data sources.

Objectives: To assess the impact of different strategies on the identification of subjects with type 2 diabetes (T2DM).

Methods: Eight data sources from Spain, Italy, the Netherlands, Denmark, the UK and Estonia were considered: three primary care (PCD), thr ee administrative (AD), one hospital (HD) and one biobank (BD). Using the Unified Medical Language System, medical concepts of pertinent diagnoses, treatments, such as insulin or non-insulin antiglycemic drugs (NIAD) or laboratory tests (glycated hemoglobin ≥6.5%) were selected and projected to local terminologies. In each data source, a list of component algorithms to be used as inclusion or exclusion criteria was extracted and their individual contribution to the identification of subjects with T2DM in 2012 in patients older than 16 was assessed.

Results: Subjects with a record of T2DM diagnosis were 4.6%, 6.3% and 6.6% in PCD, 0.9%, 1.5% and 3.2% in AD, and 3.9% in BD and 16.0% in HD. In two of three AD, drug utilization was the main source of case identification, as such data sources contained diagnoses only from the hospital inpatient environment. In fact, in these two AD, adding subjects with at least two records of NIAD increased the total number of cases about 3.5-fold, while adding both NIAD and insulin, after excluding patients with diagnoses of other indications (type 1 diabetes and gestational diabetes), increased the number 3.6- to 4-fold. In two out of three PCD, adding subjects with at least two records of glycated hemoglobin ≥6.5% increased the number of cases identified of 5% and 40%, respectively.

Conclusions: Case identification strategies have an important impact on the size and type of patient population identified and should be clearly documented to provide the necessary context for interpretation. In multi-data source studies, harmonization of event identification is a substantial process, due to differences and availability of data in each source.

941. Refinement of a Generalized Natural Language Processing Algorithm for the Identification of Clinical Terms from Free-Text Clinical Notes

Anthony P Nunes, Kathleen M Mortimer, Jeanne Loughlin, Florence T Wang, David D Dore. *Optum Epidemiology, Waltham, MA, USA.*

Background: Clinical notes within electronic health records (EHR) may contain information absent from structured data, including medical and social history, and reports of medical encounters outside the EHR system. Diagnoses recorded within clinical notes may enable identification of outcomes without a dedicated diagnostic code, such as binge eating disorder (BED). Natural language processing (NLP) facilitates identification of conditions or treatments of interest; however, validation of NLP algorithms is warranted.

Objectives: To describe the validation of a generalized NLP algorithm, using BED as an applied example.

Methods: A priori clinical terms suggestive of BED (including 'binge eating disorder', 'binge–purge', 'bulimia', and related erroneous or alternative spellings) and corresponding sentiments (e.g., negation, attribution to family members, or recommendation to avoid) were identified from clinical notes using a generalized NLP algorithm. Within the sample of clinical notes in 1 month , the NLP outputwas compared to verbatim text segments for the purposes of validation.

Results: Within the sample of clinical notes, 1144 mentions of BED-related terms were identified. Comparison of NLP output to verbatim text suggests that reliance on NLP identified sentiments can accurately exclude many non-cases. Of 19 explicit mentions of 'binge eating disorder', 4 (21%) was accurately negated and 15 (79%) was not negated [9 (47%) with active BED, 4 (21%) with insufficient text to determine, and 2 (11%) with resolved BED]. Review of verbatim text associated with more general terms ('binge eating' and 'binge–purge') identified mentions with insufficient information to distinguish present or potential conditions (e.g., checklists of potential patient problems that contained 'binge eating').

Conclusions: NLP classification based on a generalized approach identified patients with binge eating

disorders (active or historical); however, misclassification may occur due to ambiguous text. Review of verbatim text segments provides insight for the refinement of the identification algorithm through targeted NLP development.

942. Validation of Treatment Codes in the Danish National Patient Register

Uffe Heide-Jørgensen,[1] Maja Hellfritzsch,[1,2] Henriette Kristoffersen,[1] Vera Ehrenstein.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Prescription registries typically lack data on hospital treatments. The Danish National Patient Register (DNPR) uses codes for drug classes or active substances to identify certain medications administered in hospitals. Codes that have been validated generally have high positive predictive value (PPV), but sensitivity is seldom assessed. Electronic medical records (EMR), expected to reflect complete in-hospital treatment history, offer such possibility.

Objectives: To estimate PPV and sensitivity of selected DNPR treatment codes using EMR as the gold standard.

Methods: We conducted the study in the central region of Denmark, in 2007–2013. Using data linkage, we constructed cohorts of patients with metastatic cancer (MC), prostate cancer (PC), postmenopausal osteoporosis (PMO), or lung cancer (LC). For the patients with MC, PC, and PMO, we searched the DNPR and EMR for treatment codes of denosumab and zoledronic acid; for patients in the LC-cohort, we searched for treatment codes of erlotinib.

Results: Among 2107 patients with MC, 124 had a record of denosumab treatment in EMR, and 30 in DNPR (28 in both, PPV [95%CI] 93% [78–99%]; sensitivity [95%CI] 23% [16–31%]). Seven hundred seventeen MC patients had a record of ZA treatment in EMR, and 409 in DNPR (385 in both, PPV 94% [91–96%]; sensitivity 54% [50–57%]). Among 6132 PC patients, 446 had a record of denosumab treatment in EMR, and 40 in DNPR (38 in both, PPV 95% [83–99%]; sensitivity 8.5% [6.1–12%]). Fifty-six PC patients had a record of ZA treatment in EMR, and 29 in DNPR (18 in both, PPV 62% [42–79%]; sensitivity 32% [20–46%]). Among 42,826 women with PMO, 38 had a record of denosumab treatment in EMR, and 37 in DNPR (2 in both, PPV 5.4% [0.7–18%]; sensitivity 5.3% [0.6–18%]). Three hundred sixty-one women with PMO had a record of ZA treatment in EMR, and 161 in DNPR (112 in both, PPV 70% [62–77%]; sensitivity 31% [26–36%]). Among 7292 LC patients, 253 had a record of erlotinib treatment in EMR, and 260 in DNPR (110 in both, PPV 42% [36–49%]; sensitivity 44% [37–50%]).

Conclusions: Treatment codes from DNPR have low sensitivity in capturing the true use of the assessed drugs when compared against EMR.

943. The Use of Heatmaps for the Visualisation of Secular Trends of Data Completeness for Individual Variables: A Study Using the R Shiny Package

Eduardo Hermosilla,[1] Josep Maria Elorza,[1] Manuel Medina-Peralta,[2] Daniel Prieto-Alhambra.[1,3] *[1]SIDIAP Database, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain; [2]Sistema d'Informació SISAP, Institut Català de la Salut, Barcelona, Catalonia, Spain; [3]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, Oxfordshire, UK.*

Background: Data completeness is one of the dimensions of quality in routinely collected databases. Methods for the representation of data missingness over time are needed for a better understanding of the usefulness of individual variables as collected in actual practice settings.

Objectives: To test the use of heatmaps and a web aplication, as depicted using the R Shiny package, for the visual demonstration of trends in data completeness.

Methods: Setting: primary care computerised records for >80% of the population of Catalonia (>5 million subjects).

Study period: 2004–2013

Participants: All subjects registered in the SIDIAP database at any time in the study period.

Measurements: number of values registered per day for the following: body mass index, smoking, cholesterol (cT) and estimated glomerular filtration rate (eGFR).

Statistics: was used to produce heatmap for each variable Low numbers are represented in red, medium in orange and high numbers in green. The *x*- axis of the plot is week number (1 to 52), and y-axis depicts day of the week (Mon to Fri).

Results: A total of18,966,570 values of BMI were registered in 3.98 million subjects; 13,160,164 values of smoking in 4.16 million patients; 15.630.786 values of cholesterol in 3.93 million patients and 4,254,322 values of eGFR in 1.88 million participants. Heatmaps on our web application demonstrate the improvement in data completeness for all fourvariables, as well as they depict the acquisition of laboratory results from 2007 onwards, and the progressive uptake of eGFR calculations since 2011 (serum creatinine was routinely used <2011). The red colouring of bank holidays adds credibility to the recorded date of coding.

Conclusions: A web application (produced using the Shiny package in R) containing automatically updated heatmaps allows for the visualisation of secular trends and monitoring of measurement(s) completeness in routinely collected data.

944. Automatic Identification of Stages of Type 2 Diabetes, Hypertension, Ischaemic Heart Disease and Heart Failure from Italian General Practitioners' Electronic Medical Records: A Validation Study

Rosa Gini,[1,2] Martijn Schuemie,[3,4] Giampiero Mazzaglia,[5] Francesco Lapi,[5] Paolo Francesconi,[1] Alessandro Pasqua,[6] Carmelo Montalbano,[6] Valentina Barletta,[1] Iacopo Cricelli,[6] Claudio Cricelli,[5] Mariadonata Bellentani,[7] Miriam Sturkenboom,[2] Niek Klazinga.[9] *[1]Agenzia Regionale di Sanità della Toscana, Florence, Italy; [2]Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Epidemiology, Janssen Research & Development, Titusville, NJ, USA; [4]Observational Health Data Sciences and Informatics, New York, NY, USA; [5]Società Italiana di Medicina Generale, Florence, Italy; [6]Genomedics, Florence, Italy; [7]Agenzia Nazionale Per i Servizi Sanitari Regionali, Rome, Italy; [8]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.*

Background: The Health Search/Cegedim Strategic Data Longitudinal Patient Database (HSD) is an initiative of the Italian College of General Practitioners (SIMG), a scientific society of Italian General Practitioners (GP), and is similar to GP databases in the UKand other countries. This study was initiated by MATRICE, an Italian national project, to assess the ability of national data sources to detect cases of chronic diseases.

Objectives: To assess whether type 2 diabetes (T2DM), hypertension, ischaemic heart disease (IHD), heart failure (HF) and their levels of severity can be automatically detected in the population of HSD.

Methods: Clinical definitions of T2DM, hypertension, IHD and HF were established. For the first three conditions, three to five severity levels were identified. Cases were extracted automatically with a strategy combining matching on diagnostic codes and keywords, and results from diagnostic tests. An external validation of a random sample of cases was performed through direct questionnaire to GPs. An invitation to participate in the study was circulated by SIMG, and participation was voluntary. Positive predictive value (PPV) was assessed for the presence/absence of each condition, and Cohen's kappa was estimated for agreement on the severity level.

Results: A total of 12 GPs submitted data for the study. Three hundred patients were assessed for each disease, except for HF, where due to low prevalence of the condition, only 243 patients were assessed. PPV was 100% for T2DM and hypertension, 98% for IHD and 55% for HF, respectively. Cohen's kappa for levels of severity was 0.70 for T2DM and 0.69 for both hypertension and IHD.

Conclusions: This study supports use of automatic queries on HSD to detect cases of T2DM, hypertension or IHD. Automatic queries for severity levels of the same diseases compare well with the corresponding clinical definitions, but some misclassification occurs. For HF, results from automatic queries must be interpreted with caution.

945. Identifying Chronic Conditions from Data Sources with Incomplete Diagnostic Information: The Case of Italian Administrative Databases

Rosa Gini,[1,2] Martijn Schuemie,[3,4] Alessandro Pasqua,[5] Patrizio Dazzi,[6] Emanuele Carlini,[6] Massimo Coppola,[6] Iacopo Cricelli,[5] Valentina Barletta,[1] Paolo Francesconi,[1] Francesco Profili,[1] Francesco Lapi,[7] Andrea Donatini,[8] Mario Saugo,[9] Giulia Dal Co,[10] Mariadonata Bellentani,[10] Niek Klazinga,[11] Miriam Sturkenboom.[2] *[1]Agenzia Regionale di Sanità della Toscana, Florence, Italy; [2]Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands; [3]Janssen Research & Development, Titusville, NJ, USA; [4]Observational Health Data Sciences and Informatics, New York, NY, USA; [5]Genomedics, Florence, Italy; [6]Istituto di Scienza e Tecnologie*

dell'Informazione, Consiglio Nazionale delle Ricerche, Pisa, Italy; [7]Società Italiana di Medicina Generale, Florence, Italy; [8]Assessorato Politiche per la Salute, Bologna, Italy; [9]Sistema Epidemiologico Regionale Regione Veneto, Padua, Italy; [10]Agenzia Nazionale Per i Servizi Sanitari Regionali, Rome, Italy; [11]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

Background: Italy has 60 million inhabitants and a universal coverage healthcare system. Each Local Health Unit (LHU) collects administrative data about health care delivered to the inhabitants of its community. The data model of Italian Administrative Databases (IAD) is common across the country: information is collected on inpatient care, dispensed drugs, delivery of diagnostic exams and secondary care. Diagnostic codes are not collected during outpatient specialist encounters nor during primary care. In the past years, several algorithms were proposed to identify patients with chronic conditions in IAD from discharge diagnoses, drug utilization or utilization of other healthcare services. The national Italian project MATRICE initiated this study to establish optimal strategies.

Objectives: To identify optimal strategies to detect subjects with type 2 diabetes (T2DM), hypertension and ischaemic heart disease (IHD) from IAD.

Methods: In each of five LHUs, five general practitioners (GPs) with good quality clinical medical records were chosen, and case identification of the three conditions from their medical records was considered as a gold standard, on the basis of a previous study. IAD data of the same patients were collected as well. A set of algorithms combining discharge diagnoses and utilization of drugs or other healthcare services was validated against the gold standard. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values were estimated.

Results: A total of 33,995 subjects aged 16+ years entered the study. According to the gold standard, 2854 (8.4%) had T2DM, 11,332 (33.3%) had hypertension and 1419 (4.2%) had IHD. Algorithms with best balance had sensitivity, specificity, PPV and NPV, respectively, 76%, 99%, 86%, 98% for T2DM, 73%, 93%, 83% e 87% for hypertension and 63%, 98%, 79% e 99% for IHD.

Conclusions: For the three conditions, algorithms are available with excellent specificity and good PPV and NPV, but sensitivity lower than 80% and, in the case of IHD, lower than 65%. Studies on T2DM, hypertension and IHD and based on IAD need to perform sensitivity analysis to assess possible selection or misclassification bias.

946. Evaluating CPRD GOLD Recording Sensitivity of Selected Chronic Conditions Recorded in HES Hospital Data

Amy Matcho, Patrick Ryan. *Epidemiology Analytics, Janssen Research & Development, LLC, Raritan, NJ, USA.*

Background: General practitioners (GPs) in Clinical Practice Research Datalink (CPRD) GOLD are expected to enter details from inpatient stays into the medical record, but it is uncertain how well this convention is followed. A specific area of interest is whether chronic comorbidities that are observed in the Hospital Episode Statistics (HES) data are found in the GP record. The CPRD OMOP Common Data Model (CDM) can facilitate comparison of these two disparate data sources.

Objectives: CPRD GOLD recording sensitivity will be calculated for selected chronic conditions recorded in HES hospital data as a primary diagnosis.

Methods: The study population will be GOLD patients with selected HES primary inpatient diagnoses representing the chronic conditions of Alzheimer's, cerebral infarction, lung cancer, ischemic heart disease, diabetes, chronic obstructive pulmonary disease, hypertension, schizophrenia, osteoporosis and rheumatoid arthritis. We estimated the sensitivity of GOLD recording of HES primary inpatient diagnoses (assuming HES primary inpatient diagnoses are the gold standard) for each of these conditions, based on the presence of Read code in CPRD corresponding to the ICD10 code in HES as mapped within the CDM through SNOMED. We used all observed patient time, including medical history, within CPRD to assess whether the HES diagnosis was identified in the CPRD record.

Results: Of the 10 chronic conditions evaluated, six had sensitivity >80%. The lowest GOLD inpatient recording sensitivities found were 60% for ICD10 codes representing Alzheimer's and cerebral infarction. The highest GOLD inpatient recording sensitivities found were 94% for ICD10 codes representing type 2 diabetes and rheumatoid arthritis.

Conclusions: Selected chronic prevalent conditions represented by HES primary ICD10 diagnoses are fairly well captured in the GOLD data. The CPRD GOLD-HES linkage, facilitated by standardized mapping to the OMOP CDM, provides a unique data resource to evaluate operating characteristics of diagnoses.

947. An Audit of Patients Transferred Out of the Health Improvement Network (THIN) – A UK Primary Care Database

Melissa Myland, David Ansell, Ahmed Nasser, Fiona Hill, Caroline J O'Leary.
CSD MR UK, London, UK.

Background: When patients leave a primary care practice, their status is changed to 'inactive', the transfer date is recorded in their electronic medical records and their information ceases to be updated at that practice. For research purposes, the date of transfer provides an end date for the patient's record and allows follow-up time to be calculated. No prior study has profiled the population of patients transferred out of THIN while exploring trends over time.

Objectives:
- To investigate the yearly age and sex variations of patients transferring out of THIN.
- To quantify the impact of transferring patients on THIN data research.

Methods: THIN patients with a status of 'transferred out' for any reason other than death between 2000–2013 were included in this study. The numbers of patients transferring each year were split by age (in 5-year age bands) and sex. These patients were compared to mid-year counts of the THIN population for that year to determine the percentage within each group transferring out.

Results: Overall, the annual percentage of patients transferring out of THIN has gradually decreased (7.2% in 2000, 6.7% in 2013). The proportion of patients transferred was not constant across all age groups. The highest proportion of transfers were found in three age groups: 0–4 years (avg percentage transferring: 9.6%, SD: 0.7%), 20–29 yrs (avg: 13.8%, SD: 0.9%) and 95+ years (avg: 11.0%, SD: 2.8%). The age distribution of patients transferring yearly did not change appreciably.

Conclusions: Peaks in proportions transferred out of THIN may be explained by increased mobility in certain age groups. Families with young children (0–4 years) may relocate more often, especially after new births. Young adults (20–29 years) may be relocating for education, employment, or purchasing a new home. The elderly may transfer to residential/care homes served by a different practice. The reduction in overall transfers per year may represent a genuine trend and this, together with death rate analyses, will be the subject of further investigation.

948. The Incidence of Solid Tumors in a Healthcare Database Compared To SEER

Chintan Dave,[1] Jinghua He,[2] Almut Winterstein,[1] Abraham Hartzema.[1] [1]*Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA;* [2]*Merck & Co., Inc., North Wales, PA, USA.*

Background: Prior validation studies suggest that in identifying incident cases of cancer, reliance on diagnostic codes in healthcare claims data might result in low positive predictive value.

Objectives: To estimate the incidence rate of four solid tumors (female breast, prostate, lung, and colorectal) in a healthcare database and compare them to estimates obtained from the SEER cancer registry.

Methods: We used MarketScan commercial claims data for years 2009–2011 for this study. All patients with an ICD9 code for a solid tumor during a 6-month look back period were excluded. We used three definitions to identify incident cancer cases: (1) two inpatient or outpatient ICD9 codes indicating solid tumor diagnosis, (2) one inpatient or two outpatient ICD9 codes indicating solid tumor diagnosis, and (3) one inpatient or two outpatient claims where at least one cancer code was required to be the primary code. In instances where two ICD9 codes were utilized, we required them to be at least 30 days but no more than 6 months apart. We created 10 age and sex strata. For each cancer type, overall and stratum-specific incidence rates were calculated and compared with stratum-specific SEER rates. We calculated an overall SEER incidence rate using SEER rates and standardizing them to the study population by age and sex. Using definition 1 as reference, we divided the overall incidence rate obtained from claims by the overall SEER incidence rate to calculate a ratio that quantified the overestimation for each cancer type.

Results: We found the incidence rates for all solid tumors to be greater than the SEER estimates. Female breast cancer had the highest deviation from the SEER

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estimates with a calculated ratio of 8, followed by prostate cancer at 2.5, colorectal cancer at 2.3, and lung cancer at 1.6. Cancers that had high ratios also had high levels of agreement between the three definitions we used to identify incident cases. This implies that diagnostic codes might have limited utility in identifying incident cases for these cancer types.

Conclusions: Preventive diagnostic screenings might be responsible for certain cancers having an elevated ratio. In these cases, additional variables may be required to identify incident cases.

949. Development of Common Data Model Using Clinformatics Data Mart Database and Its Application in a Descriptive Analysis of Diabetes Population

Ling Zhang, Lili Wang, Jusmanda Wu, Juhaeri Juhaeri, Yunxun Wang, Ali Pasha.

Sanofi, Sanofi, Bridgewater, NJ, USA; Customer Solution Center, Metlife, Bridewater, NJ, USA; Teradata SAS Center of Excellence, Teradata, Dayton, OH, USA.

Background: Recently, the need to use multiple databases in pharmacovigilance and risk management is rising. Observational medical outcomes partnership (OMOP) and FDA have been promoting the Common Data Models (CDMs) for synchronizing various data sources as well as enabling rapid, efficient, comparable,and systematic analyses.

Objectives: The aim of this analysis is to develop the CDM using the Clinformatics Data Mart (formerly Labrx) database as well as to evaluate its application by conducting a descriptive study in a type II diabetes mellitus (T2DM) population.

Methods: The CDM intends to use a person-centric design with standardized formats to synchronizing attributes from demographics, drug exposures, and medical conditions in different databases. By following the OMOP CDM specification, the raw database of Clinformatics Data Mart was mapped into CDM by SAS or SAS-Teradata hybrid versions: identifying the specific disease population, raw data extraction, and transformation. In order to evaluate the quality of the CDM, a descriptive study on T2DM patients and the use of anti-diabetic drugs was performed.

Results: There are five regularly used datasets generated by each CDM creation: medical, drug, enrollment, demographic, and hospital records tables. With Teradata, the execution time was substantially reduced around 500 times in diabetes CDM creation. There were 2,772,084 T2DM patients identified by ICD9 codes and anti-diabetes usage. The cumulative anti-diabetic drug use was 59.2% in T2DM patients from 2000 to 2013. It was found the oral medication usage increased steadily (30% to 45%) among T2DM patients, which was parallel with the trend of insulin use (7.5% to 12.5%) across the years.

Conclusions: The advantage of CDM is to produce quick results for often used disease populations with repeated study design, which was confirmed by our test case on diabetes. After this test case, multiple diseases CDMs were created, including for 1% general population, dyslipidemia, and multiple sclerosis. By incorporating example codes, the efficiency of our work was increased.

950. Comparison of Beta Coefficient versus Risk Ratio-Based Scoring System to Assign Weights to Comorbidity Score

Hemalkumar B Mehta,[1] Vinay Mehta,[2] Cynthia Girman,[3] Michael L Johnson.[4] *[1]Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA; [2]Epidemiology, Merck, North Wales, PA, USA; [3]CERobs consulting LLC, Chapel Hill, NC, USA; [4]Department of Pharmaceutical Health Outcomes and Policy, University of Houston, Houston, TX, USA.*

Background: Scoring algorithms based on β-coefficient or risk ratio have been used widely to assign weights to different comorbidity scores or risk indices. However, no empirical evidence exists whether alteration of scoring algorithms and weighting affects the performance of a comorbidity score.

Objectives: To compare different versions of Charlson comorbidity score (CCS) derived using β-coefficient or risk ratio-based scoring systems.

Methods: Elderly people (age $\geq$65 years) from the Clinical Practice Research Database were included. Cox proportional hazards regression models were constructed for time to 1-year mortality, including 17 individual Charlson comorbidities, age and gender as predictor variables. Weights were assigned to 17 comorbidities using β and HR-based scoring systems. β-based scoring included β/integer (rounding β to the

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nearest integer), β10/integer (rounding $\beta * 10$ to the nearest integer), β/Schneeweiss (increase weight by 1 unit with each 0.3 increase in β), β/Sullivan (divide β by the smallest value of β). Charlson ($1.0 < HR < 1.5$ then weight = 1, $1.5 \leq HR < 2.5$ then weight = 2) and Johnson's scoring system were based on HRs. Weights for 17 diseases were summed to construct a summary CCS. Different versions of summary CCS were compared using c-statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI). We also simulated data and compared scoring systems.

Results: The baseline model and CCS categories model had c-statistics of 0.740 and 0.770, respectively. The β-based CCS (c-statistics range, 0.767–0.770; IDI range, 1.42–1.71) showed better discrimination compared to HR-based CCS (c-statistics range, 0.767–0.768; IDI range, 1.32–1.49). β-based CCS reclassified more number of people into correct strata (NRI range, 7.79–10.04) compared to HR-based CCS (NRI range, 8.14–8.22). Results were similar in the simulated data showing slightly better performance with β-based scoring system.

Conclusions: Use of different scoring system affects the performance of a comorbidity score. Researchers should use β-coefficient based scoring system when developing comorbidity score or risk index as it is more appropriate theoretically.

951. The Apparent Effect of Oral Contraceptives on the Risk of Venous Thromboembolism Depends on the Length of the Look-Back Period

Anders H Riis,[1] Martin B Johansen,[2] M Alan Brookhart,[3] Til Stürmer,[3] Henrik Støvring.[4] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Unit of Clinical Biostatistics, Aalborg University Hospital, Aalborg, Denmark; [3]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [4]Department of Public Health - Biostatistics, Aarhus University, Aarhus, Denmark.*

Background: Use of combined oral contraceptives (COCs) may increase the risk of venous thromboembolism (VTE) shortly after initiation of COC. A new user design can be used to characterize this risk, but if its look-back period is too short, prior users may be misclassified as new users.

Objectives: To investigate the effect of the look-back period length on VTE risk among patients initiating COC.

Methods: All women resident in Denmark on their 13th birthday in the period from 1 January 1995 until 31 December 2011 were included, except women with a history of cardiovascular disease. COC treatment status was classified as recent new use, prevalent use, former use, and compared to never users. COC treatment initiation was assessed in cohorts defined by not having redeemed a COC prescription in the look-back period, the lengths of which were varied from 1 to 10 years. Women were considered exposed to recent COC initiation 6 months after their initiation. True new use was defined as not having a prior prescription of COC after the 13th birthday. Women were followed from their 13th birthday until their first hospital admission with a diagnosis of VTE or censoring (death, emigration, or end of follow-up on 31 December 2011), whichever came first. Age was used as time-scale and COC treatment status as time-dependent exposure in a proportional hazards regression model.

Results: A total of 509,919 women were included, of whom 1294 were diagnosed with VTE during follow-up. Using a 1-year look-back period, 15.1% of these were categorized as recent initiators of COC at the time of their VTE diagnosis, which decreased to 10.1% with a 10-year look-back period. Using the true new user definition, the proportion was 10.0%. The hazard ratio (HR) for developing VTE comparing recent initiators to non-users correspondingly increased from 3.6 (1 year look-back) to 7.0 for 5 years and 8.4 for 10 years. The HR with the true new user definition was 8.8.

Conclusions: The estimated effect of recent initiation of COCs depended on the length of look-back period and is underestimated even with a look-back period of 5 years.

952. Addressing Confounding through Extreme Cohort Restriction in Large Datasets: CNODES Analysis of PPIs and Pneumonia

Dan Chateau,[1] Kristian B Filion,[2] Laura E Targownik,[3] Matthew Dahl.[1] *[1]Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada; [2]Centre for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, Montreal, QC, Canada; [3]Section of Gastroenterology,*

Division of Internal Medicine, University of Manitoba, Winnipeg, MB, Canada.

Background: The Canadian Network for Observational Drug Effect Studies (CNODES) combines populations from multiple jurisdictions to study drug safety. This allows for the use of creative approaches to cohort construction that minimize bias.

Objectives: We will illustrate how these techniques minimize confounding using a study of proton pump inhibitors (PPIs) and hospitalization for community-acquired pneumonia (HCAP). Using methods similar to previous studies, potentially biased results reappear.

Methods: Observational studies have consistently shown an association between PPI use and HCAP. However, there is a strong possibility that this association is confounded by the presence of gastro-esophageal reflux disease (GERD), the most common indication for PPI therapy, and a risk factor for pneumonia. In 2% of cases, PPIs may be prescribed prophylactically in users of non-steroidal anti-inflammatory drugs (NSAIDs), who are less likely to have GERD. By pooling data across multiple jurisdictions, a large cohort of new NSAID users concurrently prescribed a new PPI allows for an adequately powered analysis, with a minimized risk of confounding.

Results: In previous research, an intention-to-treat analysis conducted in a cohort of new users of NSAIDs found no link between PPIs and HCAP (aOR = 1.05; 95%CI 0.89 to 1.25) after adjustment using a high-dimensional propensity score. The current study confirms that these results were due to reduction of confounding by GERD. A similar analysis was conducted at one site (Manitoba) using a larger cohort of new PPI users (i.e., without the restriction to NSAID users) PPIs). PPI use was associated with HCAP when examined in the unrestricted cohort (aOR 1.27), similar to previous studies that had been unable to minimize bias through extreme cohort restriction.

Conclusions: The use of common protocol approach across multiple jurisdictions allows for research on rare exposures or outcomes that may not be possible in any individual dataset. Here, the development of a cohort of new PPI users reduced confounding, an approach that would not have been feasible in any single jurisdiction.

953. Impact of the Start of Follow-Up on Estimates of Incidence Rates of Prespecified Outcomes Following Administration of 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23)

Lina Titievsky,[1] Daina B Esposito,[2] Jennifer CL Hawes,[3] Crystal N Holick,[2] Robert Maroko,[1] Rosalind C Hollingsworth,[1] Stephan Lanes.[2] *[1]Pfizer Inc., New York City, NY, USA; [2]Safety and Epidemiology, HealthCore, Andover, MA, USA; [3]Aetion, Inc, New York, NY, USA.*

Background: Administrative claims data are widely used for evaluation of disease incidence and vaccine safety monitoring activities.

Objectives: To estimate the incidence rate (IR) of prespecified endpoints during various risk windows afterPPSV23 vaccine and explore the impact of starting follow-up on the day of versus the day after vaccination.

Methods: We identified adults who were enrolled in the HealthCore Integrated Research Database™ for at least 1 year between 2008 and 2013. For patients that received PPSV23 at least 1 year after the start of health plan eligibility, we estimated the IRs of 36 endpoints during the periods 1 day, 1 week, 2 weeks, 6 weeks, and 6 months following administration of PPSV23. We repeated analyses using two index dates: the vaccination date and the day after vaccination.

Results: A total of 389,365 adults received PPSV23 between 2008 and 2013. When follow-up started on the vaccination date, IRs for all outcomes were highest on the vaccination day and decreased dramatically and progressively thereafter. For example, the IR for hyperthyroidism was 1710 per 100,000 person-years (PYs) during the one day risk window and 136 in the six-month window. When follow-up began on the day after vaccination, however, this pattern was no longer consistent across outcomes, and most IRs became relatively stable across the risk periods. For example, the one day and six-month IRs for hyperthyroidism were each 118 per 100,000 PYs.

Conclusions: In the context of vaccine exposure and outcome associations, different definitions of index date and risk windows can have profound effects on incidence rates. For acute events with rapid onset (e.g., anaphylaxis), it is important to start follow-up on the date of vaccine administration, but assessment

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of chronic conditions (e.g., hyperthyroidism) should consider starting follow-up the day after the vaccination to reduce the likelihood of capturing prevalent conditions recorded at the index encounter but present before administration of the vaccine.

954. Exploring Methods to Measure the Prevalence of Ménière's Disease (MD) in the US Clinformatics™ Database, 2009–2012

Kristen Ricchetti-Masterson, Molly L Aldridge, Nittaya Suppapanya, John Logie, Suzanne F Cook. *Worldwide Epidemiology, GlaxoSmithKline, Research Triangle Park, NC, USA.*

Background: Literature on the prevalence of the inner ear disorder, Ménière's disease (MD) is limited. Published studies use disparate methods for sample selection, case identification, and length of observation. Prevalence estimates vary considerably between countries from 17–513 cases per 100,000 persons in Japan and Finland, respectively.

Objectives: To explore the impact of case detection strategies and observation periods in estimating prevalence of MD in the USA.

Methods: Data were obtained from the Clinformatics™ Data Mart Multiplan (IMPACT – OptumInsight Life Sciences, Inc.), a US insurance claims database. We compared prevalence estimates using case detection strategies of ≥1, ≥2, and ≥3 ICD-9 insurance claims and observation time periods of 1 (2012) and 3 years (2010–2012), with no prescription requirements.

Results: Using a case detection strategy of ≥1 ICD-9 insurance claim codes for MD within a 1-year period, the 2012 prevalence estimate was 66 cases per 100,000 persons. For ≥2 insurance claim codes, the 2012 prevalence estimate was 27 cases per 100,000 persons, and for ≥3 claim codes, the 2012 prevalence estimate was 14 cases per 100,000 persons. For ≥1 claims with a 3-year observation period, the prevalence estimate was 200 cases per 100,000 persons. For ≥2 claims, the prevalence estimate was 104 cases per 100,000 persons, and for ≥3 claims, the prevalence estimate was 66 cases per 100,000 persons.

Conclusions: Of the few available 1-year prevalence estimates from several non-US countries, results vary from 46 to 157 cases per 100,000. Our 1-year prevalence estimate calculated using ≥1 claim fell within this wide range. For the 3-year period prevalence estimate calculated with ≥1 claim, our findings are similar to previous findings in the USA. Multi-year estimates may be needed to allow for adequate follow-up time. Estimates using ≥2 claims may be the most appropriate estimate of the true prevalence of MD.Estimates based on a single claim are likely to overestimate prevalence; this is aligned with the AAO-HNS criteria requiring ≥2 definitive episodes for a definite diagnosis and has implications for future epidemiological research.

955. Hybrid Prospective Studies: Combining Existing and New Data Sources to Achieve Research Goals

Christina D Mack,[1] Ann Marie McNeil,[2] Louise Parmenter,[1] Kourtney Davis,[3] Nancy A Dreyer.[1] *[1]Real-World & Late Phase Research, Quintiles, Research Triangle Park, NC, USA; [2]Center for Observational Research & Evidence, Merck & Co, Whitehouse Station, NJ, USA; [3]Worldwide Epidemiology, GlaxoSmithKline, Upper Providence, PS, USA.*

Background: Hybrid prospective studies (HPS) combine data collected directly from physicians and patients with existing data such as medical records, insurance claims or registries. HPS provide an efficient method to incorporate difficult-to-capture data in safety, effectiveness and other outcomes research.

Objectives: To discuss strategies to leverage increasing availability of linkable clinical, administrative and patient-reported data for more powerful research approaches.

Methods: We explored design and implementation considerations for HPS, including expectations of global regulators, using case studies in diabetes, fibromyalgia and COPD.

Results: Practical considerations drive HPS design, allowing collection of treatments, comorbidities and healthcare utilization from existing sources while focusing *de novo* data collection on elements such as PROs, QoL, sensor-based data (physical activity, vitals and adherence), reasons for medication changes and biomarkers. This enables a single study to address multiple research questions and offers an opportunity to validate exposures and study endpoints. By reducing the burden of data collection, clinicians without robust research infrastructures are able to participate, resulting in more representative populations.

Operational considerations include well-defined data harmonization processes and evaluation of existing data to ensure that critical elements are of acceptable completeness and quality. Pilot studies are best practice to confirm data availability and sufficient sample size for all analysis groups. Attention to adjudication of outcomes, calculation of time windows and compliance with real-world safety reporting implications within GVP rules are also important.

Limitations of existing data sources apply to HPS, including variability at healthcare system and practice level between geographies, entities and EMR systems. Careful evaluation of data elements and qualification of partners inform decisions on managing missing data and collection of critical data elements.

Conclusions: HPS leverage existing data with *de novo* data collection to generate meaningful evidence in real-world settings while maximizing efficiency and value.

956. The Risk of Cardiovascular Events with Clarithromycin: A Comparison of Self-Controlled and Propensity Score Methodologies

Adrian A Root,[1] Angel YS Wong,[2] Yonas Ghebremichael-Weldeselassie,[3] Liam Smeeth,[1] Krishnan Bhaskaran,[1] Stephen Evans,[1] Ruth Brauer,[1] Ian CK Wong,[2] Vidya Navaratnam,[1] Ian Douglas.[1] *[1]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK; [2]Department of Pharmacology and Pharmacy, Hong Kong University, Hong Kong; [3]Department of Mathematics and Statistics, The Open University, Milton Keynes, Buckinghamshire, UK.*

Background: Studies suggest an association between clarithromycin and cardiovascular events up to 3 years later, but this could be due to indication bias. This study investigates this association in the context of Helicobacter pylori treatment (HPT), which may be less susceptible to this bias.

Objectives: Investigate the association between clarithromycin-containing HPT and subsequent first myocardial infarction (MI) in a primary care cohort.

Methods: The UK Clinical Practice Research Datalink was used to conduct this research. A self-controlled case series (SCCS) study compared the rates of first MI within the year following a clarithromycin-containing HPT with all other periods in the patient's registration. A non-parametric SCCS method where no risk windows are pre-specified was also applied. A case-time-control (CTC) study (matching on age, sex and general practice) was conducted comparing exposures in the year before first MI with the previous year. Finally, a propensity score-adjusted cohort study compared rates of first MI in 3 years following exposure to clarithromycin containing HPT to clarithromycin free HPT.

Results: SCCS analysis showed no increase in risk of first MI in the year following exposure (IRR 1.07, 95% CI 0.85–1.34, $p=0.85$). IRR functions estimated from the non-parametric SCCS method showed similar results. The CTC study showed no increase in risk for prescriptions in the year before first MI compared with the previous year (OR 0.86, 95%CI 0.59–1.26, $p=0.44$). The propensity score-adjusted cohort study showed no increased rate of first MI in 3 years after exposure to clarithromycin-containing HPT compared to clarithromycin-free HPT (RR 0.74, 95%CI 0.6–1.48, $p=0.8$).

Conclusions: There is no association demonstrated between clarithromycin-containing HPT and first MI. The previous suggestion of an association may be due to indication bias where sicker patients were preferentially treated with clarithromycin compared with the comparator antibiotic.

957. Comparing Incidence of Serious Adverse Events Between Laninamivir and Non-User of Neuraminidase Inhibitor in Influenza Patients

Shimpei Niwa,[1] Masato Fukushima,[1] Kazuhito Shiosakai,[2] Yasushi Hasebe.[1] *[1]Pharmacovigilance Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan; [2]Clinical Data & Biostatistics Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan.*

Background: Association between neuropsychiatric events such as abnormal behavior and delirium and the use of neuraminidase inhibitors (NI) remains unclear since these events may be accompanied by complications of influenza.

Objectives: To determine the incidence of serious adverse event (SAE) between the laninamivir group and the non-user of NI (non-NI) group.

Methods: We conducted a retrospective cohort study using claim data of Japan Medical Data Center, and

identified 69,697 outpatients with influenza from December 2012 to March 2013. We defined the SAE as an event related to hospitalization, which developed within 5 days after diagnosed influenza. Logistic regression was performed to compare the odds ratio (OR) and 95% confidence intervals (CI) of SAE between the laninamivir group and the non- NI group. Results were adjusted for potential confounding variables, including age, sex, and underlying diseases such as respiratory disorders.

Results: The incidence of SAE was 0.08% in the laninamivir group and 0.55% in the non-NI group (adjusted OR: 0.28, 95%CI: 0.15–0.51). Respiratory event and neuropsychiatric event were frequently observed. The incident rate of respiratory event and neuropsychiatric event were 0.04% and 0.02% in laninamivir group, and 0.30% and 0.02% in the non-NI group. The incidence of respiratory event was significantly different between the laninamivir group and the non-NI group (adjusted OR: 0.27, 95%CI: 0.12–0.63).

Conclusions: The study suggested that the risk of serious respiratory event in influenza patient might be decreased in the laninamivir group and the risk of serious neuropsychiatric event might be the same between the laninamivir group and the non-NI group.

958. Standardised Classification Not Suitable for Spontaneous Reporting: The Example of Osteonecrosis of the Jaw

Paul de Boissieu, Brahim Azzouz, Caroline Saint Martin, Thierry Trenque. *Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Reims University Hospital, Reims, France.*

Background: Osteonecrosis of the jaw (ONJ) is a well-known side effect in patients receiving bisphosphonates. In post-marketing surveillance, we observed that spontaneous adverse drug reports, which did not meet the criteria required for a standardised classification, were excluded in the analysis.

Objectives: The present study examined the impact of the use of a standardised definition of bisphosphonate-related osteonecrosis of the jaw (BRONJ) when analysing a spontaneous reporting database.

Methods: The study used data from the French National Pharmacovigilance database of adverse drug reactions. Observations reported from 1985 to 31 December 2013 were reviewed using the MedDRA term ONJ. First, we considered all reports of ONJ with bisphosphonates as BRONJ. Secondly, we applied the definition of BRONJ from the American Association of Oral and Maxillofacial Surgeons (AAOMS), namely, exposed bone persisting for more than 8 weeks, current or previous treatment with bisphosphonates and no history of radiation therapy to the jaw. In the absence of any one of these criteria, or missing data, cases were not considered as BRONJ.

Results: Up to 31 December 2013, 158 cases of ONJ, among which 153 were associated with bisphosphonate use, have been recorded in our database. According to the AAOMS criteria, 34 cases of BRONJ were selected. Exposed bone criterion was missing in 116 of the 119 excluded cases. In three cases, radiation therapy to the jaw was reported.

Conclusions: The AAOMS definition is not suitable for use in a spontaneous reporting database. When cases of ONJ are identified, all results should be presented: confirmed and excluded cases and the reason for exclusion. A clinical standardised classification is unsuitable to select cases in a spontaneous reports database of adverse drug reactions.

959. Consequences of Drugs Withdrawal: The Examples of Pioglitazone and Dextropropoxyphene in France

Cecile Pageot,[1,2,3] Julien Bezin,[1,2,3,4] Theo Larrousse,[1,3] Francesco Salvo,[1,2,3,4] Mickael Arnaud,[1,2] Francoise Haramburu,[2,3] Antoine Pariente.[1,2,3,4] *[1]Université de Bordeaux, Bordeaux, France; [2]INSERM U657, Bordeaux, France; [3]CHU de Bordeaux, Bordeaux, France; [4]CIC Bordeaux CIC1401, Bordeaux, France.*

Background: Consequences of drug withdrawal have been mostly studied considering drug prescription patterns; changes in reporting have been less often studied.

Objectives: To describe the changes in spontaneous reporting and reimbursement related to the withdrawal, for safety reasons, of pioglitazone (PGZ) and dextropropoxyphene (DPX) in France.

Methods: A cross-sectional study was performed using data from the French spontaneous reporting database and the national representative sample of the French health insurance system database. For

PGZ, DPX and some of their alternates, number of spontaneous reports (SRs), reported adverse reactions (RARs, one SR can mention several RARs), and reimbursements were compared between two periods: the 1-year period preceding the first official safety alert (PGZ: Apr-2011; DPX: Jun-2010), and 1-year following the date of withdrawal (PGZ: Jul-2011; DPX: Mar-2011). All oral anti-diabetics were considered as alternates for PGZ and step 2 analgesics for DPX. Only alternates with significant increasing of reimbursements between the two periods are presented here.

Results: After PGZ withdrawal, SRs due to DPP-4 inhibitors increased by 133%, RARs by 114% and reimbursements increased by 55%; for glinides, SRs increased by 70%, RARs by 63%, and reimbursements by 11%. For DPX, an increase in SRs, RARs, and reimbursements was observed for the two alternates: tramadol (SRs: +15%, RARs: +26%, reimbursements: +13%), and codeine (SRs: +61%, RARs: +77%, and reimbursements: +47%). For DPP4-inhibitors, the increase in RARs was mostly related to cutaneous and gastrointestinal AEs (21% and 14% of total RARs increase). For glinides, it was related to cutaneous and haematological AEs (19% and 14% of total RARs increase). For tramadol, events responsible for the increase were mostly neurological and psychiatric (23%, 15%); for codeine, they were mostly neurological and gastrointestinal (21%, 17%).

Conclusions: Whether for PGZ or DPX withdrawals, SRs increases seemed to be higher than reimbursements increases for all the alternates. One of the possible explanations of this result could be a higher occurence of AEs due to switching from the withdrawn drug to an alternate.

960. Long-Term Cancer Surveillance: Five-Year Update for the Forteo Patient Registry Surveillance Study

David Harris,[1] Alicia Gilsenan,[1] Abenah Harding,[1] Elizabeth Andrews,[1] Nicole Kellier,[2] Daniel Masica.[2] *[1]RTI Health Solutions, Research Triangle Park, NC, USA; [2]Eli Lilly and Company, Indianapolis, IN, USA.*

Background: Postmarketing safety surveillance studies can be challenging to implement, especially when the outcome of interest is a rare cancer. Interim results from an ongoing study to examine adult osteosarcoma (occurring at a rate of 2.7 cases per million population in adults in the USA) using data linkage with population-based state cancer registries are presented.

Objectives: To provide a study update of the voluntary Forteo Patient Registry, designed to estimate the incidence of osteosarcoma in patients who have received treatment with teriparatide (Forteo).

Methods: This surveillance study is a multiyear, prospective registry in the USA designed to link information from adult patients with a history of teriparatide use who enroll during the 10-year recruitment period (initiated in July 2009) with participating state cancer registries annually for 15 years (through 2024) to identify osteosarcoma cases diagnosed after patients started treatment. Patients are invited to participate through multiple pathways of communication, and enrollment is tracked by pathway type when possible. The linkage algorithm uses enrollment information (name, birth date, sex, address, telephone number, race, ethnicity, and last four digits of social security number) provided with patient consent to match with participating cancer registries.

Results: In October 2014, the fifth annual linkage was completed with 42,544 patients enrolled in the Forteo Patient Registry (equivalent to 100,400 person-years of follow-up adjusted for mortality) linked to 3171 adult cases of osteosarcoma from 41 state cancer registries (covering 92% of the US population aged 18 years and older), and no matches were found. The most common pathway leading to enrollment was the medication packaging (60%) followed by the starter kit (21%).

Conclusions: Although no incident cases of osteosarcoma among patients in the Forteo Patient Registry have been identified through the linkage process, our ability to draw conclusions after 5 years about the incidence of osteosarcoma among teriparatide users is limited due to follow-up time currently available.

961. Safety Assessment and Selection Bias: Who Uses Social Media to Communicate About Medications?

Rachael L DiSantostefano,[1] Jeffery L Painter,[1] Michele Thomas,[2] Greg Powell.[1] *[1]GlaxoSmithKline, RTP, NC, USA; [2]Blue Zone Industries, Inc., Philadelphia, PA, USA.*

Background: Increasingly, patients and caregivers use social media to share health and medication experiences, which may be useful for safety surveillance.

Objectives: To describe patient characteristics among individuals using social media to communicate about 15 GSK medicines.

Methods: From a 1-year period (1 Sept 2013 to 31 Aug 2014), social media posts naming 15 GSK medications were extracted from Facebook and Twitter. De-identified posts were categorized as being potential adverse events (proto-AEs) or mentions (not proto-AEs) using proprietary natural language processing from MedWatcher™. All proto-AEs ($n=4732$) and a 10% stratified random sample of medication mentions ($n=5828$) were manually reviewed by healthcare professionals for availability of any demographic characteristics (age group, gender, race, occupation, etc.) and safety information. Characteristics were summarized by adjudicated proto-AE status and social media source, and compared with subject characteristics of spontaneous AE reports from GSK's safety database.

Results: There were 10,560 posts including 9839 adjudicated posts (2495 proto-AEs, 7344 mentions) with 721 posts excluded (not-medication related). The majority (93.5%) were from Twitter. Overall, gender, indication, and age were determined for 42.8%, 34.1%, and 2.4% of posts, respectively. This did not vary appreciably by proto-AE status or medication, but characteristics were more frequently available from Facebook than Twitter. Gender was approximately balanced when reported. Additional subject characteristics (e.g., race, occupation, etc.) were available for ≤1% of posts. From the spontaneous reports of these 15 medications during the same period ($N=34{,}681$), gender, indication, and age, were completed more frequently than social media data, available in 94%, 67%, and 66% of the cases, respectively. Spontaneous events more frequently were reported for females (66%) than males when recorded.

Conclusions: In this 1-year study of social media medication posts, the ability to assess selection bias was limited by incomplete or missing subject characteristics. More research is needed to better understand the generalizability of safety data reported in social media.

962. A Rapid Reporting and Active Surveillance System for Adverse Drug Events Based on Electronic Medical Records: Status and Perspective

Ying Liu,[1] Yexiang Zhang,[1] Yu Yang,[2] Shengfeng Wang,[2] Renfei Fang,[2] Siyan Zhan,[2] Jianxiong Deng.[1]

[1]Guangdong Adverse Drug Reaction (ADR) Center, Guangzhou, China; [2]Peking University, Beijing, China;

Background: Post-marketing drug surveillance for adverse drug events (ADEs) in China has mainly relied on spontaneous reporting from healthcare professionals. Nevertheless, incomplete information often exists in the passively reported data, and underreporting may occur.

Objectives: We aim to develop a rapid reporting and active surveillance system for ADEs of marketed drugs based on electronic medical records (EMRs) from different hospitals.

Methods: Lucene technology offers function of full-text search. Standard databases are utilized as keywords for full-text search. Software is installed in hospital's information system to identify suspected ADE cases and capture required information automatically. Once certified by hospitals, the electronic ADE forms are automatically generated and sent to Guangdong Adverse Drug Reaction (ADR) Center simultaneously. Various algorithms were established to screen out suspected ADE cases and capture required information. Guangdong ADR center has a central database, which permits access to selected inpatient information, including laboratory results.

Results: The system has been initially established since June 2014, and currently, it works in partnership with a tertiary care hospital. Healthcare professionals in the hospital respond satisfaction with the system, and the total ADE reports have been increased by 33.82% compared to the same period of the previous year, with better quality. Whereas, there are too many drug-event cases captured by the system, and manual verification remains a huge work. Roughly, electronic medical data of 110,000 cases have been collected in the central database. The present status provides basis for signal refinement or active drug safety evaluation through automatic process.

Conclusions: The system facilitates reporting of ADEs from hospitals and enhances the speed and quality of reports. Continuing work include exploration of additional algorithms to target more exactly on suspected cases or drug-event, establishment of the common data model, development of new methodology on signal refinement, or active drug safety evaluation.

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963. Minimizing Competition Bias in Signal Detection from Spontaneous Reporting Databases

Mickael Arnaud,[1,2] Francesco Salvo,[1,2,3] Moore Nicholas,[1,2,3] Bégaud Bernard,[1,2,3] Pariente Antoine.[1,2,3] *[1]Université de Bordeaux, Bordeaux, France; [2]INSERM U657, Bordeaux, France; [3]CHU Bordeaux, Bordeaux, France.*

Background: Signal detection from spontaneous reporting can be affected by competition or masking, which is caused by selective drug-event pairs reporting. To date, two automated methods exist for minimizing competition (masking factor, MF; masking ratio, MR), but they only consider competition based on individual drugs while it can be related to class effects.

Objectives: To develop an automated method accounting for the adequate level of drug grouping for identifying competitors and to compare its performance to that of MF and MR.

Methods: Reports recorded in the French spontaneous reporting database between 2000 and 2005 were selected. Five adverse events (AEs) were considered: myocardial infarction, pancreatitis, aplastic anemia, convulsions, and gastrointestinal bleeding. For the method developed in the study (Competition Index, ComIn), competitor drugs were identified, considering either Anatomical Therapeutic Chemical (ATC) classification levels 2, 3, 4, or 5, when the proportion of reports mentioning the drug for an AE was higher than a threshold, which has been varied from 5% to 20%. For MF and MR, competitors were defined according to ATC level 5 and identified as indicated by authors. Signal detection corrected for competition bias was performed for each AE after removing reports mentioning competitors; SDRs were considered unmasked when detected only after competition correction. Unmasked SDRs were validated using Summaries of Product Characteristics (SPC); they were considered true positive if the AE was mentioned in this SPC and false positive otherwise. The set of all unmasked SDRs served as gold standard for computing performance (area under the curve, AUC; sensitivity, Se) of ComIn with each tested ATC level/threshold combination, MF and MR.

Results: From the 82,885 reports considered, signal detection identified initially 264 SDRs for the AEs studied, and 152 after correction for competition. ComIn used at ATC level 3/threshold of 12% obtained similar AUC than MF and MR, but higher Se: 57% (66 unmasked SDRs) vs. 4% for MF (4 unmasked SDRs), and 10% for MR (12 unmasked SDRs).

Conclusions: ComIn used at optimal combination suggests greatest Se for SDR unmasking than MF and MR.

964. A Review of Databases Used for Pharmacoepidemiology in China

Yang Zhang,[1] Zhi Qu,[1] Yuji Feng,[2] Kui Huang,[3] Xiaofeng Zhou,[3] Siyan Zhan,[1] Yu Yang.[1] *[1]Dept.of Epidemiology and Biostatistics, School of Public Health, Peking University Health Sicence Center, Beijing, China; [2]Epidemiology and Real-World Data Analytics, Pfizer Investment Co. Ltd., Beijing, China; [3]Epidemiology, Pfizer Inc, New York, USA.*

Background: Electronic healthcare data play a key role in pharmacoepidemiology (PE), but systematic reviews of such data in China are limited. The Observational Medical Outcomes Partnership (OMOP), a US initiative, developed a Common Data Model (CDM) with the specific aim of being a standard for all EHR and claims data.

Objectives: To provide a review of electronic healthcare databases (EHD) used for PE in China with a focus on accessible databases and to compare key data elements of the databases with those of OMOP.

Methods: A literature search through 11/1/2014 for the English articles utilized an EHD for PE research in China was performed using PubMed and EMBASE, and for Chinese articles using CNKI and Wanfang. Interviews with experts and online search (Google) for additional databases were also conducted. Only multiple centers-based databases were included. Key data elements in each accessible database were summarized and compared with those in the OMOP data tables.

Results: A total of 52 English and 793 Chinese articles were identified by PubMed and Embase, and CNKI and Wanfang, respectively. A systematic review resulted in two databases: 20 General Hospital Information System ($N=2$ million (m)) and Inpatient Drug Utilization Data ($N=0.3$ m). Expert interviews provided two additional databases: Monitoring Network for Rational Use of Drug ($N=7$ m) and Medical Insurance Database ($N=8.5$ m). Access to these four databases was granted to Peking University. Online search yielded at least nine non-accessible EHDs used (or could be used) for PE. Those are EMRs from major

tertiary and secondary hospital networks, affiliated hospitals to university, and community-based databases. Compared with OMOP data tables, a key limitation in the accessible EHDs is a lack of standard coding system for drug exposure and lab data and prevalent use of free text. Diagnosis and procedure coding quality vary widely across databases. Detailed comparisons are tabulated.

Conclusions: There have been limited published articles using EHDs for PE in China. Lack of standard coding and use of free text in EHDs have presented challenges for conducting PE studies and building CDM in China. Future work to improve the applicability of EHDs in China for PE is warranted.

965. Detecting Early Drug Safety Signals Utilizing Data from Individual Case Safety Reports and Electronic Medical Records

Kristina Juhlin,[1] Alex Asiimwe,[2] Daniel Soeria-Atmadja,[1] Susanna Cederholm,[1] David Ansell,[3] I Ralph Edwards,[1] Andrew Bate,[4] Kristina Star,[1] G Niklas Norén.[1] *[1]Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden; [2]Bayer Pharma AG, Berlin, Germany; [3]Cegedim, London, UK; [4]Pfizer, Tadworth, UK.*

Background: There is an increasing interest in electronic medical records as a possible complement to individual case safety reports (ICSRs) for signal detection. Performance comparisons to date have been restricted to well-established adverse drug reactions for positive controls.

Objectives: To compare statistical screening of electronic medical records and ICSRs against historical safety signals.

Methods: As positive controls, we used 504 drug-adverse reaction pairs corresponding to historical European labelling changes first signalled around 2004. As negative controls we used 10 080 drug-event pairs for which no MedDRA preferred term in the same high level term was listed in the Summary of Product Characteristics of that drug in 2012. Analyses were performed using primary care data from The Health Improvement Network (THIN) in the UK and the WHO global ICSR database VigiBase®, each backdated to 31 December 2004. For comparison, a subset analysis of UK reports in VigiBase was also performed. Drug-event associations were identified using the IC disproportionality measure in VigiBase, and the calibrated self-controlled cohort analysis of vigiTrace, in THIN. The predictive performance was measured as area under the receiver operating characteristics curve (AUC).

Results: The AUC values were 0.81 for VigiBase, 0.59 for the UK subset of VigiBase, and 0.49 for THIN. Only one of the positive controls was detected in THIN. An important explanation for this is that 65% of the drugs in the reference set had fewer than 100 new prescriptions overall in THIN. Many of these products are only prescribed in secondary care; others were not available on the UK market at the time, which may also contribute to the lower performance when restricting VigiBase to reports from the UK. Thirteen percent of the medical events in the reference set had fewer than 100 records in THIN. In some cases, the low event rates are explained by incomplete mapping between the MedDRA and Read terminologies.

Conclusions: Comprehensive surveillance for early safety signals requires broad population coverage as well as effective ascertainment of a wide spectrum of newly marketed drugs and adverse events.

966. Evaluation of Internet Social Networks Using Net Scoring Tool: A Case Study in Adverse Drug Reaction Mining

Sandrine Katsahian,[1,3,4,6] Agnès Lillo Le Louet,[8] Redhouane Abdellaoui,[7] Nathalie Texier,[7] Cédric Bousquet,[2,5] Abdelali Boussadi,[1,3,4,6] Carole Faviez,[7] ADR Prism Study Goup.[1,2,3,4,5,6,7,8] *[1]INSERM, UMRS 1138, Team 22, Centre de Recherche des Cordeliers, Paris, France; [2]INSERM, U1142, LIMICS, Paris, France; [3]Sorbonne Universités, UPMC Univ Paris 06, UMTS1138, Centre de Recherche des Cordeliers, Paris, France; [4]Université Paris Descartes, Sobonne Paris Cité, UMRS 1138, Centre de Recherche des Cordeliers, Paris, France; [5]Public Health and Medical Informatics, University of Saint-Etienne, Saint-Etienne, France; [6]Informatique Hospitalière, AP-HP, HEGP, Paris, France; [7]Kappa Santé, Paris, France; [8]Pharmaco-épidémologie, AP-HP, HEGP, Paris, France.*

Background: Adverse drug reactions (ADR) are a major public health problem but only 5% to 10% of ADR are supposed to be reported. Suspected adverse drug reactions reported by patients through social media can be a complementary tool to already existing ADRs signal detection processes. However, several

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studies have shown that the quality of medical information published online varies drastically whatever the health topic addressed.

Objectives: The aim of this study is to use an existing rating tool on a set of social network web sites in order to assess the capabilities of these tools to guide experts for selecting the most adapted social network web site to mine ADRs.

Methods: First, we reviewed and rated 132 Internet forums and social networks according to three major criteria: the number of visits, the notoriety of the forum and the number of messages posted in relation with health and drug therapy.Second, the pharmacist reviewed the topic-oriented message boards with a small number of drug names to ensure that they were not off topic. Six experts have been chosen to assess the selected Internet forums using a French scoring tool: net scoring. Three different scores and the agreement between experts according to each set of scores using weighted kappa pooled using mean have been computed.

Results: Three Internet forums were chosen at the end of the selection step. Some criteria get high score (scores 3–4) no matter the website evaluated like accessibility (45–46) or design (34–36), at the opposite, some criteria always have bad scores like quantitative (40–42) and ethical aspect (43–44), hyperlinks actualization (3033). Kappa were positives but very small which corresponds to a weak agreement between experts.

Conclusions: The personal opinion of the expert seems to have a major impact, undermining the relevance of the criterion. The use of social network web sites is a useful tool to assist current pharmacovigilance.

967. Cardiovascular Risk of Over-The-Counter Non-Steroidal Anti-Inflammatory Drugs in the French National Claims Database

Mai TT Duong,[1] Abdelilah Abouelfath,[2] Regis Lassalle,[2,3] Cecile Droz,[2,3] Nicholas Moore.[1,2,3] *[1]INSERM U657, Bordeaux, France; [2]INSERM CIC-P 0005 Pharmaco-Epidemiologie, Bordeaux, France; [3]Département de Pharmacologie, Université de Bordeaux, Bordeaux, France.*

Background: Over-the-counter (OTC) medications are usually not found in health insurance or electronic health records databases. There is little information on the cardiovascular risks associated with the use of OTC nonsteroidal anti-inflammatory drugs (ON). In France, ON are reimbursed if prescribed; this represents 70% of all ON use.

Objectives: Using the ON reimbursement data, this study aims to estimate cardiovascular risk associated with ON.

Methods: Cohort study in the 1/97 sample of the French National database, using paracetamol as a comparator. During 2009–2012, all new episodes of ON use were identified and matched with two paracetamol episodes on age, sex and propensity score in a range of ±0.05. Primary outcomes were admissions for myocardial infarction or unstable angina (ACS). Patients in each episode were followed up to 30 days or until an NSAID switch. Adjusted relative risk (RR) was estimated with logistic regression model after the matching procedure.

Results: A total of 236 409 ON episodes (mean age 39 years; 62% female), average exposure 7.8 days were identified and matched with 472 818 paracetamol episodes, average exposure 7.1 days. No significant association between ON exposure and ACS was found over the 30 days of follow-up: respectively 37 and 62 events (event rate 1.5 and 1.3 per 10 000 episodes, RR 1.20; 95% confidence interval: 0.80–1.80). There was a significantly higher risk in the first 2 weeks with 28 and 26 events (1.2 and 0.6 per 10 000 episodes; RR 2.17; 1.27–3.70), which corresponds to the exposure time, and a significantly lower risk in the last 2 weeks (RR 0.42; 0.19–0.96), the post-exposure period. Excess risk with ON represented 0.2 cases per 10 000 episodes over 30 days; 0.6 per 10 000 in the first 2 weeks and −0.4 per 10 000 episodes in the second fortnight. OTC ibuprofen represented 218 899 episodes, 93% of total ON use.

Conclusions: Though over 30 days there was no significant increase in risk of ACS, the risk was significantly higher in the first 2 weeks of exposure and significantly lower in the next 2 weeks of post-exposure. The reasons for this biphasic variation are unclear and warrant confirmation and further study.

968. Multidimensional Indicators for Mortality Prediction in Community-Dwelling Older People in a UK Nationwide Healthcare Database: Data from the EU-funded MPI_AGE Project

Janet Sultana,[1] Andrea Fontana,[2] Francesco Giorgianni,[1] Alberto Pilotto,[3] Miriam Sturkenboom,[4] Gianluca Trifiro'.[1,4] *[1]University of Messina, Messina,*

Italy; [2]IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [3]ULSS 16 Padova, S Antonio Hospital, Padova, Italy; [4]Erasmus University Medical Centre, Rotterdam, The Netherlands.

Background: Multidimensional indicators, that is, functional, cognitive, nutritional, and social information, in general practice (GP) databases have rarely been used in mortality prediction.

Objectives: To identify multidimensional indicators and evaluate their additional value in a previously developed primary care morbidity score (QOF) for the prediction of 1-month and 1-year mortality in elderly persons, using The Health Improvement Network (THIN), a UK nationwide GP database.

Methods: Patients ≥65 years were identified in the THIN database during 2000–2012. THIN was mined for the following multidimensional indicators: accommodation, activities of daily living, mobility, cognition, and nursing needs. 1-month and 1-year mortality was predicted using Cox models with the following covariates: (1) age + sex, (2) age + sex + QOF score, and (3) age + sex + QOF score + multidimensional indicators.

Results: A total of 1,193,268 subjects aged ≥65 years were identified (median follow-up 5.5, range: 2.5–9.9 years). The most frequently registered multidimensional indicators were mobility (4.6%), accommodation (1.98%), cognition (0.55%), and dressing ability (0.44%). Model 1 had a lower discriminatory power for mortality prediction than model 2. A significant improvement on 1-year and 1-month mortality prediction was seen by adding accommodation into the model 2: from 0.71 (0.70–0.72) to 0.75 (0.75–0.76) and from 0.72 (0.70–0.74) to 0.78 (0.77–0.80), respectively. 1-year mortality predictions for dementia patients were generally less accurate but improved from 0.62 (0.59–0.66) to 0.64 (0.61–0.68) on adding accommodation in the model.

Conclusions: Multidimensional indicators were not frequently recorded in the THIN database. Multidimensional indicators may improve the accuracy of a model incorporating age, sex, and QOF score to predict 1-month and 1-year mortality among community-dwelling older people; prediction was less marked for dementia patients. Adjusting for multidimensional indicators can significantly improve mortality prediction in pharmacoepidemiologic studies among elderly persons.

969. Breast Cancer Risk with Long-Term Use of Calcium Channel Blockers or Angiotensin-Converting Enzyme Inhibitors among Postmenopausal Women

Marsha A Raebel,[1] Chan Zeng,[1] Heather Spencer Feigelson,[1] Susan Shetterly,[1] Nikki M Carroll,[1] Kristin Goddard,[1] Denise M Boudreau,[2] David H Smith,[3] T Craig Cheetham,[4] Heather Tavel,[1] Stanley Xu.[1] *[1]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO, USA; [2]Group Health Research Institute, Group Health, Seattle, WA, USA; [3]Center for Health Research, Kaiser Permanente Northwest, Portland, OR, USA; [4]Department of Research and Evaluation, Southern California Permanente Medical Group, Pasadena, CA, USA.*

Background: Controversy exists on risk of breast cancer (BRCA) with long-term use of calcium channel blockers (CCB) or angiotensin-converting enzyme inhibitors (ACEi). Previous studies had conflicting findings, and most had small sample size or relied on self-report.

Objectives: To assess relationships between CCB or ACEi use and risk of invasive BRCA in postmenopausal women with <1 to 12 years CCB or ACEi use.

Methods: We constructed a retrospective cohort of hypertensive women aged ≥55 years from three Kaiser Permanente (KP) regions who were enrolled with pharmacy benefits ≥1 year before cohort entry. Women were new users of CCB or ACEi (i.e., no dispensing of either in prior year). Cohort entry was date of first CCB or ACEi dispensing. Analysis included women with ≥1 year follow-up. In separate models, we considered cumulative CCB or ACEi use duration as exposure and incident invasive BRCA as outcome. We used the life-table method to obtain crude BRCA hazards for 12 yearly categories of use durations and a discrete survival method to obtain hazard ratios (HR) and 95% confidence intervals (95%CI) after adjusting for covariates, both time varying (other antihypertensives, age, BMI, hysterectomy, diabetes, alcohol, estrogen, statins, and mammography) and fixed (KP region, race, education, and cohort entry year).

Results: The cohort included 29,830 (18%) women taking CCB and 135,977 (82%) taking ACEi. Mean age in years: CCB = 68; ACEi = 67. Mean body mass index (BMI): CCB = 29; ACEi = 30. Mean years (SD) on CCB = 2.6 (2.7), ACEi = 2.9 (2.9). For all comparisons, reference was ≤1 year use. In adjusted analyses, for all CCB use durations >1–12 years, the 95%CI included

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1, for example, adjusted HR for 9 years = 1.09 (0.60, 2.00) and 12 years = 0.88 (0.28, 2.78). In adjusted analyses, for all ACEi use durations >1–12 years, the 95%CI was <1, for example, adjusted HR for 9 years = 0.51 (0.37, 0.70) and 12 years = 0.54 (0.31, 0.94).

Conclusions: Compared to <1 year use, for CCB use to 12 years, we found no statistically significant increased BRCA risk. Compared to <1 year use, ACEi use to 12 years was associated with a protective effect against BRCA.

970. Risk of Acute Myocardial Infarction during Use of Individual NSAIDs: A Nested Case–Control Study in the SOS Project

Gwen MC Masclee,[1,2] Huub Straatman,[3] Ron Herings,[3] Edeltraut Garbe,[4] Tania Schink,[4] Bianca Kollhorst,[4] Andrea Arfe,[5] Silvia Lucchi,[6] Marco Villa,[6] Jordi Castellsague,[7] Susana Perez-Gutthann,[7] Cristina Varas-Lorenzo,[7] Silvana Romio,[1,5] Rene Schade,[1] Martijn J Schuemie,[1] Vera E Valkhoff,[1,2] Miriam CJM Sturkenboom.[1,8] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands; [3]PHARMO Institute, Utrecht, The Netherlands; [4]Leibniz Institute of Prevention Research and Epidemiology, Bremen, Germany; [5]University Milano-Bicocca, Milano, Italy; [6]Local Health Authority ASL Cremona, Cremona, Italy; [7]RTI Health Solutions, Barcelona, Spain; [8]Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands.*

Background: Use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of acute myocardial infarction (AMI), but the magnitude varies across individual NSAIDs and is unknown for some NSAIDs.

Objectives: To estimate the risk of AMI associated with individual NSAIDs.

Methods: Design: Nested case–control study in an adult new NSAID user cohort. Each case was matched to 100 controls on database, sex, age, and event date by using common data model and software for data transformations.

Setting: Six European healthcare datasources: IPCI, PHARMO, NL; SISR, OSSIFF, IT; GePaRD, DE and THIN, UK; 1999–2011.

Exposure: All captured NSAIDs. Dose and duration analyses were conducted in IPCI, PHARMO and THIN.

Outcome: Cases had a coded diagnosis of AMI.

Statistical analysis: Adjusted odds ratios (ORs) were estimated in each datasource for current compared to past use. Pooling was done by a random effects model (ORmeta) and combining datasets on individual level (ORpool).

Results: We matched 79,553 AMI cases to almost 7.5 million controls. Odds ratios were estimated for 28 individual NSAIDs when combining datasets on individual level. The risk was highest for ketorolac (ORmeta 2.06; ORpool 1.80) followed by indometacin (ORmeta 1.47; ORpool 1.51) then etoricoxib, diclofenac and rofecoxib (ORmeta ranged 1.26–1.31 and ORpool 1.28–1.39). Duration of use of ≥90 days and 1–6 days were associated with higher risks for various NSAIDs compared to duration of 7–29 days. Doses >1.2 times DDD for celecoxib, ibuprofen and naproxen showed higher risk estimates than normal (0.8–1.2DDD) doses. Effect modification by sex (diclofenac), age (aceclofenac, naproxen), history of ischemic heart disease (etoricoxib, ibuprofen and tenoxicam) and use of lipid-lowering drugs (diclofenac) was present.

Conclusions: The risk of AMI differed considerably for individual NSAIDs and was highest for ketorolac. An increased risk of AMI should not be considered an effect of some selective COX-2 inhibitors only.Collaboration of databases across countries with different prescription patterns enabled to yield risk estimates for a large variety of individual NSAIDS and also of infrequently used NSAIDs.

971.Fracture Healing Complication (FHC) in Women with Postmenopausal Osteoporosis (PMO) Exposed to Bisphosphonate (BP) versus Other or No Osteoporosis Medication (OPM)

Fei Xue,[1] Yessenia Bartley,[1] Victor Gastanaga,[1] Chuck Wentworth.[2] *[1]Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA; [2]Analytic Consulting Solutions Inc., Providence, RI, USA.*

Background: BP inhibits osteoclast-mediated bone resorption, prevents bone loss and improves bone strength. However, due to its inhibitory effect on osteoclastic bone resporption and the importance of osteoclasts for remodeling callus into cortical bone, it remains controversial whether bisphosphonate affects bone fracture healing.

Objectives: To compare the incidence of FHC in patients exposed to BP, other OPM or no OPM.

Methods: Women ≥55 years with ≥1 year of enrollment in the UK THIN database (1995–2012) who received a diagnosis or treatment related to osteoporosis were included in the PMO cohort. The PMO cohort was followed for incident FHC including malunion, delayed union and nonunion of bone fracture. Both intent-to-treat analysis comparing initiators of BP or other OPM to the untreated, and as-treated analysis comparing person-years with on-treatment or on- plus post-treatment of BP and/or other OPM to the untreated were conducted to assess the treatment effect of BP and other OPM on FHC.

Results: A total 246 cases FHC were identified in 170 313 women. In both age-adjusted and multivariate-adjusted analysis, a lower incidence of FHC was found in initiators of BP [IRR (95%CI) = 0.33 (0.25–0.45) and 0.31 (0.23–0.42), respectively] and initiators of other OPM [IRR (95%CI) = 0.29 (0.09–0.93) and 0.31 (0.10–0.98), respectively], relative to patients with no OPM. Similarly, a lower incidence of FHC was associated with on-treatment with BP only and other OPM only [IRR (95%CI) = 0.47 (0.35–0.64) and 0.13 (0.02–0.94), respectively]. The sample size was too small to inform the analysis of on-treatment with both BP and OPM. Similar results were found when extending the time-at-risk from on-treatment to 1- or 5-year post-treatment period.

Conclusions: Results from this study did not suggest BP treatment and other OPM may decrease the risk of FHC. However, the finding may be contaminated by the decreased risk of incident fracture due to treatment effect of BP and OPM. Future studies restricting to patients with existing fracture are warranted to clarify the effect of BP on fracture healing process.

972. Antidepressants and the Risk of Hip Fractures

Tania Schink,[1] Kathrin Jobski,[1] Niklas Schmedt,[1] Bianca Kollhorst,[1] Edeltraut Garbe.[1] [1]*Leibniz Institute for Prevention Research and Epidemiology - BIPS, Bremen, Germany.*

Background: Use of antidepressants (AD), especially tricyclic and tetracyclic ADs (TCA) and selective serotonin reuptake inhibitors (SSRI) has been associated with an increased risk of hip fractures (HFX), but studies comparing individual ADs are rare.

Objectives: To compare the risk of HFX of individual ADs in the elderly.

Methods: Based on data from the German Pharmacoepidemiological Research Database (GePaRD) from 2005 to 2011, we performed a cohort study among new users of ADs ≥65 years. Patients were followed until the first of the following events: HFX, 180 days of follow-up, or end of enrolment/study period. ADs were categorized as TCA, SSRI, monoamine oxidase inhibitors (MAO), selective serotonin noradrenalin reuptake inhibitors (SSNRI), noradrenalin reuptake inhibitors (NARI), and other ADs (including St John's wort). HFX cases were defined as hospitalizations due to a femur fracture. Multivariable Cox regression was used to estimate confounder adjusted hazard ratios (HRs). Results were stratified by sex, age, diagnosis of depression and opioid use. In sensitivity analyses, patients with a history of HFX were excluded, length of follow-up was varied, and patients were censored at end/switch of treatment. Additionally, propensity-score (PS) adjustment was used for the comparison of AD classes.

Results: We identified 439 317 new AD users ≥65 years. Median age was 72 years, and 72% were female. Compared to TCA, the use of SSRI and SSNRI was associated with an increased risk of HFX (HR: 1.58; 95% confidence interval: 1.45–1.71 and 1.43; 1.17–1.76), use of other ADs was associated with a decreased risk (0.67; 0.51–0.87). Sensitivity as well as PS-adjusted analyses yielded comparable results. Compared to citalopram use of opipramol (0.44; 0.37–0.51), trimipramine (0.48; 0.39–0.58), doxepin (0.56; 0.47–0.67), mirtazapine (0.66; 0.58–0.75) and amitriptyline (0.78; 0.70–0.87) was associated with a lower risk of HFX. Risks were similar in patients with and without depression, but the SSRI associated risk of HFX was lower in patients using opioids than in patients not using opioids.

Conclusions: Our study indicates an increased risk of HFX for SSRI and SSNRI compared to TCA. Similar effects were observed for individual SSRI suggesting a class effect.

973. Antipsychotics and the Risk of Hip Fractures

Tania Schink,[1] Niklas Schmedt,[1] Kathrin Jobski,[1] Bianca Kollhorst,[1] Edeltraut Garbe.[1] [1]*Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany.*

Background: Use of antipsychotics (AP) has been associated with a higher risk of hip fractures (HFX), but studies comparing individual APs are rare.

Objectives: To compare the risk of HFX of AP classes and individual APs in the elderly.

Methods: Based on data from the German Pharmacoepidemiological Research Database from 2005 to 2011, we performed a cohort study among new users of APs (N05A excl. lithium) ≥65 years. Patients were followed until the first of the following: HFX, 180 days after cohort entry, or end of enrolment/study period. HFX was defined as hospitalization due to a femur fracture. Multivariable Cox regression was used to estimate confounder adjusted hazard ratios (HRs) for HFX. Results were stratified by sex, age, diagnosis of dementia. In sensitivity analyses, patients with a history of HFX were excluded, length of follow-up was varied, and patients were censored at end/switch of treatment. Additionally, propensity-score (PS) adjustment was used for the comparison of AP classes.

Results: Overall, 309,273 new users of AD ≥65 years were identified. Median age was 78 years, and 68% were female. Use of conventional APs slightly increased the risk of HFX compared to atypical NLs (HR: 1.10; 95%CI: 1.02–1.18). Comparable results were found in the PS-adjusted and sensitivity analyses, whereas no statistically significant risk was observed when patients were censored at end/switch of treatment (1.03; 0.86–1.23). Compared to risperidone, significantly elevated risks were observed for haloperidol (1.35; 1.18–1.55), quetiapine (1.22; 1.04–1.44), pipamperone (1.17; 1.01–1.35) and melperone (1.11; 1.00–1.22). Use of fluspirilene (0.44; 0.35–0.55), sulpiride (0.51; 0.43–0.61) and promethazine (0.76; 0.66–0.87) was associated with a lower risk of HFX. Stratification revealed an increased risk for conventional APs in patients with dementia (1.13; 1.02–1.24), in males (1.28; 1.09–1.50) and in patients aged 85 years or older (1.26; 1.12–1.41).

Conclusions: Our study suggests a decreased risk of HFX for elderly users of atypical compared to conventional APs. Individual conventional antipsychotics were associated both with increased and decreased risks, whereas quetiapine was the only atypical AP associated with an increased risk.

974. Risk of Major Cardiovascular Events during Second-Line Antidiabetic Treatments: A Population-Based Cohort Study

Salwa S Zghebi,[1] Douglas T Steinke,[1] Martin K Rutter,[2,3] Richard A Emsley,[4] Darren M Ashcroft.[1]

[1]Centre for Pharmacoepidemiology and Drug Safety, Manchester Pharmacy School, University of Manchester, Manchester, UK; [2]Endocrinology and Diabetes Research Group, Institute of Human Development, University of Manchester, Manchester, UK; [3]Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; [4]Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, UK.

Background: Cardiovascular (CV) disease is the major cause of morbidity and mortality in type 2 diabetes patients. Results of prior observational studies of CV risk of antidiabetic regimens could be biased by not adjusting for time-varying (TV) CV risk factors.

Objectives: To compare the risk of major CV events during second-line diabetes therapies after adjusting for known CV risk factors and TV concurrent medications.

Methods: In this retrospective cohort study, patients prescribed second-line regimens during 1998–2011 post first-line metformin were identified from the Clinical Practice Research Datalink (CPRD). Propensity score analysis of demographic and clinical covariates (e.g. HbA1c, smoking, and comorbidities) predicted choice of second-line therapy. Inverse probability of treatment-weighted time-varying Cox regression estimated hazard ratio (HR) and 95%confidence intervals (CI) for developing a major CV event (myocardial infarction, stroke, acute coronary syndrome or unstable angina). The effect of TV covariate adjustment (vs static models) was tested by likelihood ratio (LR) test.

Results: After a mean (SD) 2.4 (2.0) years of follow-up, 382 major CV events occurred in 18,700 initiators of a second-line add-on to metformin of either a sulphonylurea (SU), glitazone or gliptin. More patients (66%) added SU than other agents ($p < 0.001$). Among all groups, metformin-SU starters had the highest baseline HbA1c 71.9 (16.7) mmol/mol ($p < 0.001$); body mass index (34.4 (6.8) kg/m^2) was higher in metformin-gliptin starters ($p < 0.001$). In all regimens, LR test showed a significantly improved fit with TV adjustment ($p < 0.001$). In comparison to metformin-SU regimen, the adjusted HR (95%CI) for CV events was 0.64 (0.39–1.08) when adding a gliptin to metformin; 0.77 (0.45–1.32) when adding pioglitazone to metformin; and 0.82 (0.54–1.23) when adding rosiglitazone to metformin.

Conclusions: After adjusting for known CV risk factors, all three regimens showed a lower risk of major CV events, especially metformin–gliptin starters compared to metformin-SU initiators. These were non-significant, but the study was limited by short duration of follow-up and small number of major CV events.

975. 30-Year Mortality Following Coronary Artery Bypass Graft Surgery: A Nationwide Population-Based Cohort Study

Kasper Adelborg,[1] Erzsébet Horváth-Puhó,[1] Morten Schmidt,[1] Troels Munch,[1] Lars Pedersen,[1] Henrik Toft Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark.*

Background: The long-term mortality after coronary artery bypass graft (CABG) surgery is not well-established.

Objectives: To examine 30-year mortality of CABG patients compared with a general population comparison cohort.

Methods: Linking data from Danish registries, we conducted a nationwide population-based cohort study on patients with first-time CABG surgery (1980–2009) and a general population comparison cohort matched on age, sex, and calendar year. We used stratified Cox regression analysis to compute hazard ratios as a measure of mortality rate ratios (MRRs) with 95% confidence intervals (CI).

Results: We included 51,307 CABG patients and 513,070 individuals from the general population in the study. Median follow up time was 8.9 (interquartile range 5.1–13.0) years for CABG patients. Median age was 65 (interquartile range: 58–72) years, and a minority was women (21%).

Overall, 30-year mortality risk was higher for CABG patients (89%) than for the general population (75%) especially within the first 30 days (3.7% vs 0.3 %), 11–20 years (52.4% vs 36.1%), and 21–30 years (63.6% vs 43.9%), but also within 31–364 days (3.2% vs 2.7%) and 1–10 years (31.7% vs 27.5%) after surgery/index date. Overall, the adjusted 30-year MRR was 1.20 (95%CI: 1.18–1.21). Between 30 days and 10 years, CABG patients and the general population had similar mortality risk where after the mortality risk increased for CABG patients (11–20 years MRR: 1.49, 95%CI 1.45–1.54 and 21–30 years MRR: 1.83, 95% CI: 1.66–2.01). Compared with the general population, patients with combined CABG and valve surgery had consistently elevated mortality risk throughout the 30 years. Within 30 days, CABG patients had a 29-fold, 41-fold, and 51-fold higher risk of dying from venous thromboembolism, myocardial infarction, and stroke than individuals in the general population. Across the three decades, survival of CABG patients improved.

Conclusions: Patients with CABG surgery had higher 30-year mortality than the general population, which was driven by increased mortality at 30 days, 11–20 years and 21–30 years after surgery.

976. What is the Optimal Second-Line Antidiabetic Regimen to Delay the Onset of Microvascular Complications? Application of a Marginal Structural Model

Alison K Wright,[1] Darren M Ashcroft,[1] Martin K Rutter,[2] Richard Emsley,[3] Douglas T Steinke.[1] *[1]Centre for Pharmacoepidemiology and Drug Safety Research, Manchester Pharmacy School, University of Manchester, Manchester, UK; [2]Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; [3]Centre for Biostatistics, Institute of Population Health, University of Manchester, Manchester, UK.*

Background: Within 3 years of a type 2 diabetes (T2D) diagnosis, 50% of patients will require a combination regimen, after failure of monotherapy metformin (HbA1c>48 mmol/mol). Several drug choices are available leading to uncertainty regarding the optimal treatment pathway. Suboptimal glycaemic control increases the risk and progression of diabetes-related complications.

Objectives: To determine the optimal dual therapy regimen for delaying diagnosis of a microvascular complication.

Methods: Incident T2D patients prescribed first-line metformin or sulphonylurea (SU) between 01/01/05 and 31/12/09, with progression to a dual therapy were identified from the Clinical Practice Research Datalink (CPRD). A weighted Cox regression was conducted to assess three second-line regimens; metformin/SU, metformin/thiazolidinedione (TZD) and metformin/DPP-4, on the time to diagnosis of a microvascular complication. Inverse probability of treatment weights were constructed to account for time-dependent confounders (HbA1c, BMI) and factors, which affect

glycaemic control. The Tukey–Kramer test was conducted to assess pairwise comparisons of HbA1c and BMI.

Results: Metformin/SU regimen was the most effective dual therapy for delaying the onset of microvascular events. The rate of development of these events was significantly higher for the DPP-4 combination in comparison to the SU regimen with a hazard ratio of 1.85 (95%CI: 1.53, 2.24). A TZD combination resulted in a non-significant increase of 19% in the rate of development compared to the SU combination (HR 1.19; 95%CI: 0.98, 1.47). Metformin/SU resulted in the greatest lowering of HbA1c levels (mean reduction 8 mmol/mol) in comparison to the DPP-4 and TZD regimens; with no significant differences in BMI change between regimens.

Conclusions: Metformin/sulphonylurea was shown to be the most beneficial regimen, offering the most substantial lowering of HbA1c and greatest delay in diagnosis of microvascular complications. Although the risk of hypoglycaemia was not assessed, these findings have important implications for cost-sensitive healthcare systems.

977. Validation of Endocrine Therapy Indication to Identify Breast Cancer Chemoprevention: A Feasibility Study

Hazel B Nichols,[1] Kala Visvanathan,[2] Valerie S Lee,[3] Janise M Roh,[3] Jean X Lee,[3] Till Stürmer,[1] Lawrence H Kushi.[3] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, USA; [2]Epidemiology, Johns Hopkins University, Baltimore, MD, USA; [3]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA.*

Background: Benefits of endocrine therapy for primary prevention of breast cancer (chemoprevention) are established but must be balanced against side effects (e.g., uterine cancer, stroke, and cataracts). Difficulty assessing or communicating risks and benefits, or high discontinuation rates, may contribute to low adoption of chemoprevention outside of clinical trials.

Objectives: The primary goal of this ongoing pilot study is to demonstrate the feasibility of identifying a breast cancer chemoprevention cohort using administrative, pharmacy, and electronic health record data. In addition to validating the primary indication for therapy, we will measure medication adherence and apply a risk-benefit index.

Methods: This research was conducted using records at Kaiser Permanente Northern California during 2005–2013. We sampled women ages 35–69 years with a first pharmacy fill of tamoxifen ($N=159$), raloxifene ($N=100$), or select aromatase inhibitors ($N=112$) for medical record review and abstraction (MRA) to validate the primary indication for therapy. Inclusion criteria required ≥6 months continuous enrollment prior to the first fill date and no prior breast or gynecologic cancer or other indicating condition. Preliminary results for tamoxifen are presented here.

Results: To date, MRA for 159 tamoxifen users has been completed. Of these, 78 were ineligible—the majority (97%) due to a prior history of breast or gynecologic cancer that was diagnosed and treated at non-KP facilities or was not specified in the exclusion code list (e.g., peritoneal cancer). Of 81 eligible women, 67 (83%) were validated as breast cancer chemoprevention users. Chronic breast pain was the most common non-chemoprevention indication.

Conclusions: Expansion of diagnosis codes used as exclusion criteria (e.g., additional cancer sites; V-codes for personal breast cancer history) should improve sample selection. Among tamoxifen users who met our eligibility criteria, we validated breast cancer chemoprevention as the leading indication for therapy. These initial findings support the feasibility of studying real-world breast cancer chemoprevention use in integrated healthcare settings.

978. Toward Optimizing Data Structure in Cancer Registries

Anokhi J Kapasi,[1] Varinder Singh,[1] Sharmila A Kamani,[1] Judith K Jones.[1] *[1]DGI, LLC, Fairfax, VA, USA.*

Background: Cancer is a major cause of morbidity and mortality, necessitating systematic monitoring of cancer incidence. No standard method exists for developing cancer registries. BRIDGE TO DATA® (www.bridgetodata.org), a resource of database profiles worldwide, can contribute to optimization of data collected for registries.

Objectives: To characterize cancer registries by *frequency* and *types* of data to identify gaps and

opportunities for enhancing current registries and building future ones.

Methods: A search was conducted in BRIDGE: *Database Type = Registry* and *Cancer Data = Yes*. The search yielded 191 profiles matching one criterion, 43 matching both criteria. Search results were narrowed to 20 profiles that specified "cancer registry". For each data field, frequency of usage (100%, >50%, ≤50%) among the set of registries and types of data populating the field (similar/variable) were tabulated.

Results: Of 69 data fields in the analysis, 20 were used by all 20 cancer registries: five fields captured identical data (e.g., gender), while 15 had variable data (e.g., patient type, date of birth format, death data, and source). Another 18 fields were utilized by the majority of registries (e.g., procedures and lab data). Of 31 infrequent fields (e.g., sociodemographic, physical exams, drugs), nine were not utilized by any registry (e.g., environmental exposures and cost data). Cancer registries in this analysis included nationally representative populations, were initiated before year 2000, and are systematically updated from multiple data sources. Cancer diagnoses were predominantly recorded with ICD-10/ICD-O-3 codes and variably included diagnosis date and histology/pathology data. About half captured death cause and date, primarily obtained from autopsies/death certificates. Although drug data were infrequently captured, treatment procedure data were common.

Conclusions: BRIDGE was successfully used to analyze and categorize data fields in these cancer registries and may serve as a template when designing or improving future registries. Infrequently captured data may prove important for understanding diseases relating to exposures (e.g., environmental and drugs), and may enhance quality of cancer studies (e.g., cost of illness studies).

979. Validity of Inhospital Mortality Records in the National Health Insurance Research Database among Patients with Acute Myocardial Infarction and Stroke Cases in Taiwan

Ching-Lan Cheng,[1] Cheng-Han Lee,[2] Swu-Jane Lin,[3] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; [3]University of Illinois at Chicago, Chicago, IL, USA.*

Background: Our previous studies showed that the positive predict value (PPV) on primary diagnose of acute myocardial infarction and ischemic stroke in National Health Insurance Research Database (NHIRD) were more than 90%, thus deemed the database appropriate for research in this disease area. However, record of death have not yet validate in NHIRD since death certification file is not provided by the National Health Research Institution.

Objectives: The aim of this study was to determine the validity of record of inhospital mortality in the NHIRD by cross-comparisons of death records listed in the electronic database from a medical center in Taiwan.

Methods: This was a cross-sectional study, comparing records in NHIRD and electronic database in one medical center (EMC). Patients who had admissions for acute myocardial infarction (AMI) or stroke during year 2005 to 2010 were extracted from the two databases. PPV for death records were evaluated by linkage the data recorded in the medical center. We also estimated the insurance status and death record in catastrophic files in confirmed death cases. Agreement in comorbidities between the two databases was evaluated.

Results: A total of 6197 cases with a linkage rate of 96.56%, including 1500 AMI, 1373 hemorrhage stroke and 3324 ischemic stroke. Five hundred thirty-eight of 682 patients had death record ("4","5","A") in NHIRD were confirmed death record by using EMC as gold standard, which yielded a PPV of 0.79. Three hundred sixty-four patients had death record in both catastrophic files and EMC, which yielded a percentage positive agreement (PPA) of 76%. The percentage of consistency in comorbidity diagnoses was more than 0.9 among matched AMI cases, except chronic kidney disorder.

Conclusions: The accuracy of death records in NHIRD was high, and the agreement between NHIRD and EMC in recording comorbidity diagnosis was over 90%. NHIRD appears to be a valid resource for population research in cardiovascular diseases.

980. Development and Validation of the RxDx-Dementia Risk Index TO Predict Dementia in Patients with Type 2 Diabetes and Hypertension

Hemalkumar B Mehta,[1] Vinay Mehta,[2] Chu-Lin Tsai,[3] Hua Chen,[4] Rajender R Aparasu,[4] Michael L

Johnson.[4] *[1]Department of Surgery, University of Texas Medical Branch, Galveston, TX, USA; [2]Epidemiology, Merck, North Wales, PA, USA; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Pharmaceutical Health Outcomes and Policy, University of Houston, Houston, TX, USA.*

Background: Five risk indices are available to predict the risk of dementia. They include diagnosis, lab or genotype information but none includes prescription drug information.

Objectives: The objective of this study was to utilize diagnosis and prescription drug information to develop and validate an RxDx-dementia risk index to predict dementia in patients with type 2 diabetes mellitus (T2DM) and hypertension (HTN).

Methods: Elderly patients (age≥65 years) diagnosed with T2DM and HTN without a prior diagnosis for dementia were selected from the Clinical Practice Research database ($N = 133\,176$). The Cox proportional hazard model was constructed to model time to dementia by incorporating age, gender and 31 RxDx disease conditions. A disease was identified as RxDx disease if a patient had either diagnosis or a prescription drug specifically used to treat that condition. Points were assigned to risk factors based on β-coefficients to obtain a summary risk score. Discrimination and calibration of the risk index were evaluated using c-statistics and Hosmer-Lemeshow (H-L) chi-square statistics, respectively. The model was internally validated using 10-fold cross-validation approach. Different risk indices were compared against RxDx-dementia risk index using c-statistics, net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results: The incidence of dementia was 3.42% in patients with T2DM and HTN. The c-statistics value for RxDx-dementia risk index was 0.806 (95%CI, 0.798–0.814). The H-L statistics showed poor calibration ($p < 0.001$). Based on the c-statistics, NRI and IDI values, the RxDx-dementia risk index (c, 0.806) performed better compared to Charlson comorbidity score (c, 0.782, NRI, −6.5%, IDI, −1.9%), chronic disease score (c, 0.789; NRI, −5.9%; IDI, −1.7) and its combinations (c, 0.789; NRI, −5.9%, IDI, −1.7%).

Conclusions: In addition to diagnosis, prescription drug information can be used to improve the risk adjustment performance. The RxDx-comorbidity risk index may be useful for prognostic purpose and to control for confounding in studies where dementia is an outcome.

981. Publication of Clinical Drug Trials: An Inception Cohort Study in the Netherlands

Cornelis A van den Bogert,[1,2,3] Patrick C Souverein,[1] Cecile TM Brekelmans,[2] Susan WJ Janssen,[3] Manon van Hunnik,[3] Gerard H Koëter,[2] Hubertus GM Leufkens,[1] Lex M Bouter.[4] *[1]Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Faculty of Science, Utrecht, The Netherlands; [2]Central Committee on Research Involving Human Subjects (CCMO), The Hague, The Netherlands; [3]Division of Nutrition, Medicines and Consumer Safety, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [4]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands.*

Background: Transparency (i.e., reporting of all results of clinical trials) in clinical trials is important for evidence-based care provision and prevention of unnecessary new trials.

Objectives: To assess occurrence and determinants of publication of clinical drug studies reviewed in 2007 by Institutional Review Boards (IRBs) in the Netherlands.

Methods: We identified all clinical drug trials reviewed by the Dutch accredited IRBs between 1 January 2007 and 31 December 2007. Data were obtained on the unique study identification number, study sponsor (industry or academia), number of centers (single or multi), study phase (phase 3 or other phase), study goal (therapeutic or non-therapeutic), study type (intervention or observational), participant category (adult and mentally capacitated or minor/mentally incapacitated), registration status of involved drugs (unregistered or registered), type of drug (regular or advanced therapy), and therapeutic area (oncology or other). We used a validated search algorithm to identify scientific publications.

Results: We included 622 studies in the cohort. Overall, 44% of the studies were published seven years after IRB-approval. Publication percentages were statistically significantly lower among academic sponsors (Relative risk (RR) 0.65; 95% confidence interval (CI) [0.47, 0.90]), single center studies (RR 0.35; 95%

CI [0.25, 0.49]), other phase studies (RR 0.37; 95%CI [0.26, 0.53]); and non-therapeutic studies (RR 0.47; 95%CI [0.33, 0.65]). The other study characteristics were not associated with publication.

Conclusions: More than half of the clinical drug studies reviewed by IRBs in the Netherlands remained unpublished 7 years after approval. This finding is consistent with previous literature and emphasizes the need for more transparency.

982. Presence of Type 2 Diabetes Mellitus Diagnoses in Different Types of Healthcare Databases – Empirical Evidence from Ehr and Claims

Zhiwen Liu,[1] Yong Chen,[1] Michael Senderak,[1] Edward A Bortnichak.[1] [1]*Merck Research Laboratories, North Wales, USA.*

Background: Due to distinct purposes for health management, disease diagnoses recorded in electronic health record (EHR) and claims system may be presented differently and the difference, when presents, may have huge implications on how to use them for research. However, there is limited quantitative evidence to directly illustrate the presence of diagnoses between EHR and claims.

Objectives: To characterize the presence of type 2 diabetes mellitus (T2DM) diagnoses in an EHR and claims database.

Methods: We identified incident T2DM subjects (≥18 years of age) with a minimum 365-day continuous enrollment prior to their first T2DM diagnosis or abnormal glucose test (AGT) in the Clinical Practical Research Datalink (CPRD) and Optum Clinformatics Data Mart (CDM) from 01/01/2003 to 30/11/2013 (CPRD) or to 31/3/2014 (CDM). The subjects who had other types of diabetes or prescriptions/pharmacy records related to anti-diabetes prior to the index date were excluded. We counted the number of distinct T2DM diagnoses (no. of diagnoses) for each subject during follow-up, and stratified descriptive statistics by number of diagnoses.

Results: We identified 165 865 and 531 437 incident T2DM subjects from CPRD and CDM, respectively. CPRD had older population comparing to CDM (median 63 vs. 52 years of age) and longer average follow-up (median 4.6 vs. 1.5 years). In CPRD, 76% of subjects had only one diagnosis in entire follow-up (the subjects had number of diagnoses from 1 to 4+ are 76%, 14%, 3%, and 4%). The subjects, who had at least one AGT, or use of any anti-diabetes medications during follow-up (T2DM activities), vary very slightly by number of diagnoses (from 92% to 99%). In CDM, two peaks appear (the subjects who had number of diagnoses from 1 to 4+ are 44%, 13%, 7%, and 36%), and the subjects who had follow-up T2DM activities vary largely from 6% to 71% by number of diagnoses. In both databases, only a few subjects had AGT but not any diagnoses.

Conclusions: In our empirical T2DM sample, we demonstrate that the diagnoses are presented very differently between an EHR and claims. More result and implications including potential factors for difference will be further discussed.

983. Treatment-Related Adverse Events Recorded in Administrative Claims Compared to Electronic Medical Records

Debra E Irwin,[1] Helen Varker.[2] [1]*Truven Health Analytics, Durham, NC, USA;* [2]*Truven Health Analytics, Cambridge, MA, USA.*

Background: Existing treatments for colorectal cancer (CRC) are effective; however, patients frequently experience adverse events (AEs). Observational studies often use administrative claims data or electronic medical records (EMR) to assess AEs.

Objectives: The purpose of this analysis is to compare AEs recorded in claims data with those recorded in an oncology EMR.

Methods: Metastatic CRC cases in the MarketScan Commercial and Medicare (claims) ($n = 3144$) and the MarketScan Oncology EMR databases ($n = 804$) who received treatment with capecitabine, oxiplatin, fluorouracil, or bevacizumab were included. The index date was the first date of medication administration and patients were followed for 3, 6, and 12 months for adverse events including neutropenia, diarrhea, hand and foot syndrome (HFS), and mucositis/stomatitis (MS). Claims data patients were required to be continuously enrolled, and EMR patients were required to remain under care in the practice during the follow-up period.

Results: At 6 months follow-up, neutropenia was recorded less often in claims data (19%) compared to EMR data (29%). Neutropenia is monitored by oncologists with lab values, and this may lead to more frequent recording of less severe neutropenia in the EMR which is not reflected in claims data. The proportion with MS and HFS was about the same in claims (MS 3%; HFS 3%) compared to EMR data (MS 4%; HFS 3%). Diarrhea was recorded more often in the claims (14%) compared to the EMR (11%). Diarrhea is a common symptom and patients may seek care outside of their oncology practice; hence, claims data may capture additional diagnoses assigned by other clinicians. Similar patterns were seen at 3 and 12 months follow-up.

Conclusions: AEs monitored by lab values were recorded more often in EMR compared to claims data. Other AEs were documented in similar proportions of patients in EMR and claims data. One exception was diarrhea which was recorded more often in the EMR. Further research is needed to understand the strengths and limitations of using administrative claims data and EMR data for studying oncology related AEs.

984. Improving Control for Confounding by Frailty When Estimating Influenza Vaccine Effectiveness in Older Adults

Henry T Zhang,[1] Leah J McGrath,[2] Richard Wyss,[1] Alan R Ellis,[3] Til Sturmer.[1] *[1]Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]RTI Health Solutions, Research Triangle Park, NC, USA; [3]Social Work, North Carolina State University, Raleigh, NC, USA.*

Background: The estimation of influenza vaccination effectiveness in older adults is hampered by considerable uncontrolled confounding by frailty, leading to implausible all-cause mortality reductions.

Objectives: To improve control of confounding by frailty by (1) adding a published set of claims-based frailty predictors to the adjustment set and (2) using a modification of the high-dimensional propensity score algorithm to select pre-vaccination codes that predict mortality prior to influenza season (a negative control outcome).

Methods: We conducted an observational cohort study with U.S. Medicare claims data from 2007 to 2008. A cohort of beneficiaries >65 years of age was followed beginning 1 September 2007, covariates were assessed in the 6 months prior to follow-up, and patients were followed throughout the 2007–2008 influenza season. We estimated Cox proportional hazards models of all-cause mortality with influenza vaccination as a time-varying exposure. We controlled for a usual set of 39 baseline variables, and then separately added (a) 20 published frailty predictors and (b) 300 codes identified by the automated algorithm. We used pre-influenza season hazard ratios (HRs), which should be 1.0, to gauge residual confounding.

Results: A cohort of 2 141 713 beneficiaries was created for the 2007–2008 influenza season, resulting in 1 421 335 person-years of follow up. In this cohort, 52% were vaccinated and 5% died during follow-up. In the unadjusted model, the HR during the pre-influenza season period was 0.39(0.36, 0.41). The model with baseline variables resulted in an HR of 0.44(0.41, 0.48). Adding the frailty predictors to the baseline model moved the HR to 0.46(0.43, 0.49), whereas adding the 300 algorithm-selected codes to the baseline model resulted in an HR of 0.48(0.45, 0.51).

Conclusions: Results from the baseline model were consistent with those in the published literature, with significant uncontrolled confounding. Both approaches to controlling for frailty moved the pre-influenza season HR slightly closer to the null, but since there should be no vaccination effect prior to influenza season, it appears there is still substantial residual confounding.

985. Simulation Study of Analysis of an Open-Label Trial with Time-Dependent Confounders/Mediators

Heidi Moseson,[1] Khaled Sarsour,[2] Neil Collinson,[3] Katie Tuckwell,[3] Micki Klearman,[2] Eric Vittinghoff.[1] *[1]University of California at San Francisco, San Francisco, CA, USA; [2]Genentech, South San Francisco, CA, USA; [3]Roche Products Ltd., Welwyn Garden City, UK.*

Background: Drug developers increasingly use observational data to estimate treatment effects at reduced cost. Marginal structural models (MSMs) were developed to estimate causal effects without bias in the presence of time-dependent confounders/mediators (TDCMs) that both confound and mediate the effects of treatment. However, MSMs may be less efficient than simpler methods.

Objectives: To use simulation to compare the bias and power of MSMs and adjusted pooled logistic regression (PLR) for assessing the effects of alternative anti-inflammatory regimens.

Methods: Our simulation modeled the effects of steroids only, study drug only, and both on remission after flare-up of disease activity in patients with a form of chronic inflammation. In the simulation, treatment was initiated and could be changed in response to the TDCM. Remission was assessed at monthly visits. We simulated 500 samples of 250 patients, followed until remission or censoring at 24 months.

Results: In the presence of a moderately strong TDCM, the MSM was almost unbiased (bias, −5.8%), whereas PLR badly underestimated treatment effects (bias, −26.7%). PLR, however, had substantially greater power (93.6% vs 72.4%), with no inflation of the type I error rate. With a weaker TDCM, the bias of the PLR was smaller, but it remained more powerful than the MSM.

Conclusions: MSMs estimate treatment effects almost without bias in the presence of a TDCM but are less powerful than the simpler adjustment methods, which are biased but more precise. When clinical investigators are interested in only the relative performance of treatment regimens, the simpler PLR method may be justifiable for treatment evaluations based on observational data because it preserves the type I error rate and is biased toward the null.

986. Using Area over the Curve of Absolute Neutrophil Count to Estimate Severity and Duration of Chemotherapy-Induced Neutropenia and Relationship with Infection Risk

Yanli Li,[1] Zandra Klippel,[2] Xiaolong Shih,[3] Hong Wang,[4] Maureen Reiner,[2] John H Page.[2] *[1]Amgen Inc., South San Francisoc, CA, USA; [2]Amgen Inc., Thousand Oaks, CA, USA; [3]SimulStat Incorporated, San Diego, CA, USA; [4]TechData Service Company, LLC, King of Prussia, PA, USA.*

Background: In clinical research, it is often necessary to measure more than one dimension of an exposure to optimally capture its relationship to an outcome. Neutrophils are defensive immune cells. Neutrophil count falls after chemotherapy (chemo) and subsequently rises after bone marrow recovery. In addition to absolute neutrophil count (ANC), duration of chemo-induced neutropenia (CIN) is also important in mediating infection risk.

Objectives: To estimate severity and duration of CIN using area over the curve (AOC) of ANC and understand their quantitative relationships with infection risk among chemo-treated cancer patients

Methods: Individual data from adult non-myeloid cancer patients receiving no granulocyte colony-stimulating factor (G-CSF) during the first cycle of myelosuppressive chemo from six Amgen-sponsored clinical trials were combined. AOC of ANC was calculated as the area below clinical threshold of 0.5×10^9/L (or 1.0×10^9/L) and above the ANC-time response curve in the first chemo cycle. Time-dependent Cox proportional hazards model was used to quantify the hazard of first infection associated with AOC.

Results: Our study analyzed data from 271 patients with small cell lung cancer, non-Hodgkins lymphoma, oral cavity/ pharyngeal cancer, or breast cancer. Median (interquartile) ANC was 5.24 $(3.90–6.90)\times10^9$/L at baseline and 0.08 $(0.03–0.32)\times10^9$/L at nadir. Median time to reach ANC nadir was 13 days. 18.8% had infection-related hospitalization in the first chemo cycle. Each unit (day $\times10^9$/L ANC) increase of AOC (below 0.5×10^9L and below 1.0×10^9/L) was associated with significantly increased risk of infection-related hospitalization (HR: 1.98; 95%CI: 1.35–2.90 and HR: 1.42; 95%CI: 1.17–1.72), respectively.

Conclusions: Increase in AOC of ANC is associated with higher infection risk in chemo-treated cancer patients. When duration of an exposure below or above a threshold is predictor of outcome, a composite measure for severity and duration of the exposure, AOC or area under the curve, can be used to estimate its relationship with a relevant outcome.

987. Reducing and Quantifying Over-Fitting in Regression Models

John Rigg,[1] Matthew Hankins.[1] *[1]Real-World Evidence Solutions, IMS Health, London, UK.*

Background: Regression models are the multivariable analytical method of choice for epidemiologists and statisticians. It is widely recognized that these models may suffer from over-fitting, where the sample estimates fail to generalise to other samples. Systematic approaches to minimise over-fitting are

seldom adopted, and there is a reluctance to hold data back for independent assessment of model performance.

Objectives: This study assesses penalized regressions for reducing over-fitting, cross-validation on training data for estimating over-fitting, and the extent to which over-fitting produces misleading conclusions.

Methods: Data were extracted from the IMS PharMetrics Plus US medical claims database for patients with multiple sclerosis receiving one of two treatments. Cohorts were matched using propensity scoring, producing 3348 matched pairs. The probability of relapse and persistence were estimated using standard, stepwise and (LASSO) penalized logistic regressions. Over-fitting was measured as the difference between the area under curve (AUC) for training and test data and additionally estimated using cross-validation on training data alone.

Results: Penalised logistic regressions greatly reduced over-fitting compared to standard and stepwise alternatives, irrespective of the choice of response variable and degrees of freedom: for example, modelling relapse with 50% of the data used for training and 50% used for testing showed over-fitting of 9.9% with standard, 8.0% with stepwise and 3.9% with penalized logistic regression. Cross-validation provided reasonable approximations for over-fitting; estimated over-fitting for the above standard logistic model was 10.4%. Over-fitting inflated the estimated treatment effect by approximately 20% (OR = 2.03 vs. 1.64; standard logistic model vs. penalized model).

Conclusions: Penalized logistic regression models had substantially lower over-fitting. Moreover, good estimates of over-fitting can be derived without withholding data. Both penalized regressions and cross-validation are straightforward to implement in most statistical packages and greater adoption of these methods is encouraged to ensure more reliable estimates of risk factors.

988. A Novel Multi-Modal Approach to Stroke Care Quality Improvement and the Development of High-Performing Stroke Care Teams

Aaron Kamauu,[1,3] Mark Loveless.[1,2] *[1]Stroke Systems Analytics, Salt Lake City, UT, USA; [2]Alpha~R Systems, Portland, OR, USA; [3]Anolinx, Salt Lake City, UT, USA.*

Background: The clinical outcomes and quality of care in acute ischemic stroke (AIS) are time-dependent and influenced by the effectiveness and efficiency of the care delivery system. Much attention has been given to improving process and procedure; however, the structure and inter-dependencies of the stroke care teams must be integrated into any clinical quality improvement (CQI).

Objectives: The objective of this study was to apply an innovative multi-modal analytic approach that combines formal epidemiologic analysis, process evaluation and social network modeling of stroke care teams to evaluate actual stroke care at hospital units against the critical system characteristics of high-performing units in real-world hospital systems.

Methods: Characteristics of individual hospital units, as well as variation of treatment delivery, were analyzed and compared. A critical path analysis was created based on a widely adopted acute stroke care process model. Stroke care team structures and inter-dependencies were mapped based on the responses to a survey, and the responses were analyzed using open source network analytic software.

Results: The care team networks were overlaid to the corresponding process pathways to create a final synthesis of the process and team structure. Critical path analysis, combined with mapping of the individual stroke team network interactions, demonstrated associations between the team structures and the process/clinical outcomes. For example, lack of effective interaction between the stroke team and the pharmacy at one institution results in slower timing from thrombolytic order to administration to the patient. Opportunities for improvement in both process and personnel organization were identified and integrated into existing CQI efforts.

Conclusions: Multi-modal systems analysis incorporating both care process and stroke care team inter-dependencies offers an enhanced approach to integrated quality improvement for acute stroke care.

989. The Importance of Competing Risks in Predictive Modelling of Hip Implant Survival: A Cohort Study Using Computerised Records and Registry Data

Albert Roso,[1] Cristian Tebe,[2,3] Gary Collins,[4] Andrew Judge,[4,5] M Kassim Javaid,[4,5] Montse Rué,[6] Mireia

Espallargues,[2] Daniel Prieto-Alhambra,[1,4,5] PRESS-UP Study Investigators.[1,2,4] *[1]SIDIAP Database, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain; [2]Registre Catala d'Artroplasties (RACat), Agencia de Qualitat i Avaluacio Sanitaries de Catalunya, Generalitat de Catalunya, Barcelona, Catalonia, Spain; [3]Statistical Advisory Service, Bellvitge Biomedical Research Institute-IDIBELL, Universitat de Barcelona, Barcelona, Catalonia, Spain; [4]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK; [5]MRC Lifecourse Epidemiology Unit, Southampton University, Southampton, UK; [6]Ciencies Mediques Basiques, IRBLLEIDA, Universitat de Lleida, Lleida, Catalonia, Spain.*

Background: C>ompeting risk (CR) with death is a known limitation of Cox regression. We hypothesized that failing to account for CR can bias variable selection and/or risk estimates in predictive modelling.

Objectives: We aimed to compare the predictors identified in a prediction tool (PT) derived using Cox versus Fine and Gray (competing risk regression) analyses, as well as the performance of the resulting PTs.

Methods: Setting and participants: data from e-records and pharmacy dispensations for >5 million participants in Catalonia (www.sidiap.org) were linked to the Catalan Arthroplasty Registry. Patients in the linked dataset aged ≥40 years undergoing total hip arthroplasty in June 2005 to 2012 were included. Those with previous hip fracture or malignancy were excluded.

Event of interest: 5-year hip implant survival.

Competing Event: all-cause death.

Potential predictors: age, sex, body mass index, smoking, alcohol drinking, Charlson co-morbidity index (CCI), healthcare resource use, hip prosthesis characteristics, hospital volume, drugs used in the previous year, and indication.

Statistical analysis: Standard Cox regression and Fine and Gray models (FG) using backwards stepwise elimination ($p=0.1$) were used to identify key predictors in the PT. Performance of the PTs was assessed by c-index (discrimination) and observed/predicted agreement plots for risk deciles (calibration). Multiple imputations with 10 imputed datasets were used to handle missing data.

Results: Of 11 427 individuals, 277 (2.4%) individuals had implant revision, and 588 of 11 427 (5.2%) died during the 5-year follow-up. Cox and FG identified similar key predictors of implant survival, except for CCI that was only present in the Cox-derived PT. Discrimination was moderate and similar for both models, but FG produced better fit for the data as seen in observed/predicted plots.

Conclusions: By accounting for differential mortality, FG-derived PT eliminated a known risk factor for mortality (CCI), which had been incorrectly identified as a predictor of implant survival in Cox models. In addition, FG models had better calibration than Cox-derived PTs but moderate discrimination.

990. A Simulation Study to Explore Bias Generated When Conditioning on an Intermediate Variable That Is Also a Time-Varying Confounder

Yan Cheng,[1] Marlene Egger,[2] Wei Chen,[3] Joanne LaFleur,[1] Brian Sauer.[3] *[1]Department of Pharmacotherapy, University of Utah, Salt Lake City, UT, USA; [2]Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, USA; [3]Department of Internal Medicine, University of Utah, Salt Lake City,UT, USA.*

Background: Traditional analytic techniques are well known to produce biased results when time-dependent confounding that are intermediate variables exists.

Objectives: To generate a counterfactual simulation to compare traditional regression methods versus marginal structural models with inverse probability weights (IPW) in handling time-depended confounding biases and measuring causal treatment effect.

Methods: We simulated counterfactual data for all treatment combinations among newly diagnosed HIV patients. We followed each individual from baseline T0 through time point 2 (T2), and assumed no patient dropped out or were lost to follow-up. A1 and A2 indicated binary treatment during T0 to T1 and T1 to T2. Y(a1 = 0, a2 = 0), Y(a1 = 1, a2 = 0), Y(a1 = 0, a2 = 1) and Y(a1 = 1, a2 = 1) were used to indicate the potential death outcome if an individual would have received a specific treatment strategy. L0 and L1 represented CD4 T-cell counts at T0 and T1. We assumed A had no treatment effect on Y. A longitudinal observational study was mimicked with A(k), L(k), Y(k) predicted by L($k-1$) where $k=1$ or 2. Modified Poisson regression with adjusting for baseline and

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time-dependent covariates was used to estimate treatment effect on death. IPW weighting was also applied to evaluate the treatment effect using intention-to-treat (IIT) and as-treated (AT) approaches.

Results: After adjusting for L0 and L1, the rate ratio (rr) for partially treated (A1 = 0 and A2 = 1 or A1 = 1 and A2 = 0) versus untreated (A1 = 0 and A2 = 0) was 1.10 (95%CI 1.06–1.15), $p < 0.001$; the rr for fully treated (A1 = 1 and A2 = 1) versus untreated was 1.09 (95%CI 1.05–1.14), $p < 0.001$. In comparison, IPW weighting approaches yielded the most near unbiased estimate of the treatment effect (A = 1 vs A=0):1) ITT with unstabilized IPW: rr = 0.99 (95%CI: 0.97–1.02), $p = 0.5$; 2) ITT with stabilized IPW: rr = 0.99 (95%CI: 0.97–1.01), $p = 0.45$; 3) AT with unstabilized IPW: rr = 0.99 (95%CI: 0.97–1.02), $p = 0.77$; 4) AT with stabilized IPW: rr = 1.02 (95%CI: 1.00–1.04), $p = 0.05$.

Conclusions: The IPW approach can address time-dependent confounding bias with providing unbiased estimate of marginal effect than traditional regression models.

991. Parametric Time-To-Onset (TTO) Modelling of Common ADRs in Patients Using Antidiabetic Drugs

Joep HG Scholl,[1] Peter M van de Ven,[2] Eugène P van Puijenbroek.[1,3] *[1]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands; [2]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; [3]Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, The Netherlands.*

Background: Although the time-to-onset (TTO) is an important aspect in causality assessment of adverse drug reactions (ADRs), limited information about it is available in publicly available literature.

Objectives: The aim of this study was to investigate whether the TTO of common ADRs of antidiabetic drugs could be modelled using parametric distributions and whether these distributions were dependent on patient characteristics.

Methods: We performed an exploratory TTO modelling study, using an existing observational cohort of diabetes mellitus patients. Four parametric distributions (exponential, lognormal, gamma and Weibull) were compared in terms of their goodness of fit using the Akaike information component (AIC) and evidence ratios. Covariates that could influence the TTO (sex, age group and suspected concomitant medication) were investigated using two-sample Kolmogorov–Smirnov testing.

Results: For the antidiabetic drugs metformin, sulphonylurea (SU) derivatives and dipeptidyl peptidase-4 (DPP-4) inhibitors, a total of 441 ADRs were included for analysis. These consisted of reports concerning diarrhoea (n=255), nausea (n=127) and dizziness (n=59). Overall, the gamma distribution provided the best goodness of fit, although differences with the Weibull distribution were negligible in some instances. No statistically significant differences in TTO distributions for any of the covariates, or between different antidiabetic drugs for a given ADR, were found. Mean and median TTO values were similar for different drug-ADR combinations.

Conclusions: Our study shows that the TTO of common ADRs associated with antidiabetic drugs can be modelled using the gamma or Weibull distribution. These models can be used as a concept for the development of a structured approach to study the timing of events, and thus the causality assessment of ADRs. Furthermore, the results seem to indicate that a causal relationship between drug and ADR should not be dismissed based on a long TTO alone.

992. Dynamic Channeling among Initiators of a Recently Marketed Medication for Type 2 Diabetes Mellitus (T2DM)

Elisabetta Patorno,[1] Chandrasekar Gopalakrishnan,[1] Olesya I Zorina,[2] Sebastian Schneeweiss,[1] Dorothee B Bartels,[2] Jun Liu,[1] John D Seeger.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Corporate Department of Global Epidemiology, Boehringer Ingelheim GmbH, Ingelheim, Germany.*

Background: Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor recently marketed for T2DM treatment. Patient characteristics that influence prescription selection may evolve rapidly for such new medications, with implications for confounding control.

Objectives: To evaluate changes in the baseline characteristics of patients initiating linagliptin during the

year after launch to assess effects on propensity score (PS) estimation.

Methods: Within a large, US health insurance database (Optum Clinformatics), we identified T2DM patients initiating linagliptin or other non-insulin diabetes medications from May 2011 (the first month of linagliptin's US availability) through June 2012. We divided this study period into four consecutive time-blocks of approximately equal size, and for each time block, we assessed the baseline characteristics of drug initiators. The relative likelihood of receiving linagliptin versus another diabetes medication was estimated in a series of PS models, each based on more than 100 baseline characteristics, and the discrimination (c-statistic) and PS distributions were determined.

Results: Of 155,345 T2DM patients who initiated a non-insulin diabetes agent during the study period, 2820 patients (1.8%) initiated linagliptin. In the first time-block, linagliptin initiators had average age of 55.1 years, 58.3% of them were males, 4.8% had a diagnosis of ischemic heart disease (IHD), 3.5% had congestive heart failure (CHF), 12.8% had chronic kidney disease, and 7.8% had cancer. In the last time-block, they were older (56.1 years), less frequently male (55.6%), and less frequently had IHD (3.7%), CHF (1.7%), chronic kidney disease (10.9%), or cancer (7.1%). These changes in the baseline characteristics were reflected by decreasing c-statistics from the first to the last time-block, and increasingly overlapping PS distributions relative to each comparator.

Conclusions: Baseline characteristics of linagliptin initiators changed over the year following its launch, and these changes affected PS estimation. Dynamic channeling should be expected and accounted for in evaluations of newly marketed medications.

993. An Evaluation of the Multinomial Propensity Score in a Simulated Drug-Drug Interaction Study

Christopher G. Rowan,[1] Warren B. Bilker,[2] Jason Roy,[2] Sean Hennessy,[2] James Lewis,[2] Daniel Mines,[3] Brian L Strom.[4] *[1]Anceta Learning Collaborative, American Medical Group Association, Alexandria, VA, USA; [2]Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]Epidemiology, Merck, Upper Gwynedd, PA, USA; [4]Biomedical and Health Sciences, Rutgers, Newark, NJ, USA.*

Background: The propensity score (PS) was developed to control for differences in observed covariates for two treatment groups. In drug-drug interaction (DDI) studies, there are usually more than two non-ordered exposure categories representing a multinomial exposure. The theoretical framework for the multinomial propensity score (mPS) has been developed elsewhere.

Objectives: Our objective was to evaluate the statistical performance of the mPS as a method to adjust for confounding bias in a simulated DDI study.

Methods: Monte Carlo simulations were performed on a synthetic cohort with a non-ordered multinomial exposure arising from two primary exposure variables and one exposure interaction variable (i.e., the product term of the two primary exposure variables). Confounding and model misspecification, using three covariates independently associated with the primary exposure variables and a binary outcome variable, were introduced to evaluate statistical performance in the presence of known bias and model misspecification. The estimated beta coefficient (i.e., the interaction ratio (I*R)) for the exposure interaction variable was the primary effect estimate. We estimated the I*R using mPS adjustment, binary PS adjustment, and multivariate (MV) adjustment under a variety of simulated conditions common to empiric drug safety research. Statistical performance was assessed by determining bias, coverage probability, and precision of the estimated I*R compared to the true I*R (i.e., determined by the investigator).

Results: Under all scenarios evaluated, confounding adjustment with the mPS demonstrated excellent statistical characteristics – similar to the rarely identifiable, perfectly specified MV model. Binary PS methods, not accounting for the multinomial exposure, showed less than optimal performance.

Conclusions: Investigators conducting DDI research with a non-ordered, multivariate exposure, under similar conditions to those evaluated in this study may consider the mPS a valid confounding adjustment method.

994. Comparison of Calipers for Matching on the Disease Risk Score

John G. Connolly,[1] Joshua J. Gagne.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, USA.*

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Background: Many studies have compared calipers for propensity score (PS) matching, but none have considered appropriate calipers for matching on the disease risk score (DRS) which may have different considerations.

Objectives: We compared the performance of different calipers when used for DRS matching.

Methods: We used Medicare data from two US states to perform two new user cohort studies: raloxifene versus alendronate on 1-year fracture risk; and coxibs vs. non-selective non-steroidal anti-inflammatory drugs (ns-NSAIDs) on 6-month gastrointestinal bleed risk. For each patient, we calculated a DRS (from a model fit in the comparator drug initiators) and a prognostic PS (PPS), which is a simple transformation of the DRS calculated by including it as a sole independent variable in a PS model. We used an optimal nearest-neighbor algorithm to match patients on each score in a variable ratio within a set of eight calipers – three based on the standard deviation (SD) of the logit of each score (i.e., $0.3 \times SD$, $0.2 * SD$, $0.1 * SD$) and five based on the natural scale of each score (0.05, 0.025, 0.01, 0.001, 0.0001). In each matched population, we performed logistic regression conditional on the matched sets to estimate odds ratios (ORs), which were compared to benchmark estimates identified in the literature (OR, 1.05 for raloxifene and 0.88 for coxibs).

Results: In the raloxifene study, PPS (OR, 1.02; 95% CI, 0.91–1.15) and DRS matching both using a caliper of 0.0001 (OR, 1.02; 95%CI, 0.90–1.14) produced estimates closest to the benchmark. Matching on the PPS with a caliper of 0.05 produced an OR of 0.94 (95%CI: 0.84–1.06), which was furthest from the benchmark. In the coxibs study, PPS matching using a caliper of 0.025 (OR, 0.95; 95%CI, 0.80–1.14) produced an estimate closest to the benchmark. DRS matching with a caliper of 0.05 produced an estimate furthest from the benchmark (OR, 1.02; 95% CI, 0.85–1.21).

Conclusions: When variable-ratio matching on a DRS using an optimal nearest neighbor algorithm, calipers smaller than 0.05 and calipers based on a fraction of the SD of the logit of the DRS performed well in two examples. When using such calipers, matching on the PPS did not offer an advantage over matching directly on the DRS.

995. Non-Collapsibility and Selection Bias of Hazard Ratio

Menglan Pang,[1] Michal Abrahamowicz,[2] Robert W Platt.[2] *[1]Centre for Clinical Epidemiology, Jewish General Hospital/Lady Davis Institute, Montreal, QC, Canada; [2]Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada.*

Background: Non-collapsibility of the hazard ratio (HR) can be induced by a nonlinear relationship between the covariate and the hazard when omitting a covariate in a Cox model. Meanwhile, selection bias may be also present when an important risk factor is not included. Propensity scores can be used to control for confounding in observational studies. In longitudinal studies, the propensity scores are usually estimated from a pooled logistic regression. However, if selection bias occurs over time, residual confounding might be present with the pooled propensity score.

Objectives: To assess the non-collapsibility effect and selection bias of HR simultaneously in the Cox model when a risk factor is omitted. To investigate the performance of an alternative propensity score estimation in a longitudinal study.

Methods: We used a longitudinal simulation study to simultaneously investigate the impact of (1) the non-collapsibility effect and (2) the selection bias of the HR when omitting a time-fixed risk factor. These effects were evaluated in scenarios with a variety of treatment effects and covariate effects. For the second objective, we estimate time-specific propensity scores using the subjects at risk at each time interval only. We then compared the performance of two inverse probability-weighted Cox models that used (i) the pooled propensity score and (ii) the time-specific propensity score. We illustrate the problem in the example of statin use and acute kidney injury.

Results: Our results suggested that omitting an important risk factor resulted in substantial changes in the Cox model estimates. This change was mostly explained by the non-collapsibility effect, whereas selection bias was barely present in our simulation settings. On the other hand, both inverse probability weighted models provided unbiased estimates of the true marginal HR with comparable precision in all of our simulation scenarios.

Conclusions: In longitudinal studies with time-dependent exposure, the HR estimated from the Cox model

was not subject to the built-in selection bias, while it shifted towards null due to the non-collapsibility effect from omitting an important risk factor.

996. Historical Data for Augmenting High Dimensional Covariate Selection

Hiraku Kumamaru,[1] Joshua J Gagne,[1] Robert J Glynn,[1] Soko Setoguchi,[2] Sebastian Schneeweiss.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Duke Clinical Research Institute, Duke University, Durham, NC, USA.*

Background: High-dimensional propensity scores (hdPS) can be limited when the number of outcomes is small, such as in studies of newly marketed drugs.

Objectives: To determine whether augmenting hdPS covariate selection with historical data improves confounding control in low outcomes settings using two comparative studies of newly marketed medications: dabigatran versus warfarin on mortality and coxibs versus non-selective NSAIDs on gastrointestinal bleeds.

Methods: We constructed concurrent cohorts of new and comparator drug initiators, and historical cohorts of comparator drug initiators using US claims database. We randomly sampled with replacement 500 sets of smaller cohorts from the concurrent cohorts at different sampling fractions. We constructed five hdPS models with different covariate selection approaches: two novel approaches augmenting covariate–outcome associations from historical data, standard bias-based approach and its variant with zero-cell correction for covariate–outcome association, and one based on covariate–exposure association only. We estimated odds ratios (ORs) after stratifying on deciles of each hdPS and compared mean ORs from the 500 cohorts across the sampling fractions.

Results: The unadjusted OR for dabigatran versus warfarin was 0.38 [95% confidence interval: 0.26–0.55]. In cohorts based on 20% and 30% sampling fractions (mean total outcome events 32 and 48, respectively), the degree of adjustment by standard bias-based hdPS was smaller than in the 100% cohorts (OR, 0.69 [0.22–1.58] and 0.71 [0.30–1.47], respectively, vs. 0.80 [0.53–1.19]). Augmenting bias-based covariate selection with covariate–outcome associations in the historical data lead to consistent ORs across sampling fractions (range: 0.80–0.84). In the coxibs example, this historically augmented bias-based hdPS and the standard bias-based hdPS both performed well even in small cohorts. In both examples, bias-based hdPS with zero-cell correction yielded similar estimates to the historically augmented bias-based hdPS; other methods were less consistent.

Conclusions: In studies of newly marketed drugs with few outcomes, the use of historical data may lead to reliable empirical covariate selection and improved confounding control.

997. Comparison of Zero-Cell Correction Factors for the High-Dimensional Propensity Score Algorithm in Studies with Few Outcomes

Hiraku Kumamaru,[1] Joshua J Gagne,[1] Robert J Glynn,[1] Wesley Eddings,[1] Soko Setoguchi,[2] Sebastian Schneeweiss.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Duke Clinical Research Institute, Durham, NC, USA.*

Background: High-dimensional propensity scores (hdPS) can be limited in studies with few outcomes. Using a zero-cell correction (i.e., addition of a small value to all cells of 2×2 tables when any cell has zero observations) in assessing covariate–outcome associations has been proposed to overcome this, but the optimal value of the correction factor has not been determined.

Objectives: To empirically compare different zero-cell correction factors for hdPS in settings with few outcomes.

Methods: Using a US claims database, we formed a cohort of dabigatran and warfarin initiators after dabigatran came onto the market. To create cohorts with different numbers of outcomes, we randomly sampled with replacement 500 smaller cohorts at four sampling fractions (20%, 30%, 40%, and 100%). In each of the cohorts, we constructed five bias-based hdPS models from pre-specified plus 300 empirically identified covariates selected using different correction factors (0 [i.e., no correction], 1, 0.5, 0.1, and 0.01) for covariate–outcome association assessment. We estimated odds ratios (ORs) for mortality stratifying on deciles of each hdPS and compared mean ORs for each hdPS across the 500 cohorts at each sampling fraction. The benchmark OR was 0.93.

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Results: The crude OR for death for dabigatran versus warfarin was 0.38 (95% confidence interval: 0.26–0.55) in the whole cohort and the hdPS-adjusted OR with no correction was 0.80 (0.53–1.19). In 20% and 30% cohorts (mean total outcomes of 32 and 48, respectively), ORs with no correction were smaller (0.69 [middle 95% of distribution: 0.22–1.58] and 0.71 [0.30–1.47], respectively). Correction factors of 1 and 0.5 yielded larger ORs in the smaller cohorts (0.67 [0.19–1.77] for 1 and 0.68 [0.21–1.82] for 0.5 in 20% cohorts). Correction factors of 0.1 and 0.01 yielded ORs closer to the benchmark across all sampling fractions (range: 0.79–0.83 for 0.1 and 0.84–0.91 for 0.01).

Conclusions: In a single example, smaller hdPS zero-cell correction factors resulted in estimates closer to assumed truth. As compared to larger correction factors and no correction, small factors may lead to better hdPS covariate selection when outcomes are few.

998. The ACCE Method for Estimating Unmeasured Confounding

Eric G. Smith.[1,2] *[1]Center for Healthcare Organization and Implementation Research and Mental Health Service Line, Edith Nourse Rogers Memorial Veterans Affairs Medical Center, Bedford, MA, USA; [2]Department of Psychiatry, University of Massachusetts Medical School, Worcester, MA, USA.*

Background: Unmeasured confounding limits nonrandomized studies and may be amplified by some methods.

Objectives: To determine whether confounding amplification (if predictable, as suggested by recent research) can be used to estimate unmeasured confounding.

Methods: A method is described using two propensity score models identical but for one added variable or set of variables that generate confounding amplification. Unmeasured confounding (except that due to the variable(s) added) can then be estimated by extrapolation backwards. The observed change in the treatment effect estimate between the models is adjusted for the change in confounding due to increased balance in the added variable(s) (as estimated by an added variable(s)-outcome regression coefficient and the Bross equation), and divided by the degree of confounding amplification expected, as predicted by $1-R^2$ from linear probability propensity score models. This estimate and the original confounding due to the added variable(s) prior to its inclusion is subtracted from the smaller model's treatment effect estimate to yield an unconfounded estimate. Numerous uncertainties exist, however, including the predictability of confounding amplification in real-world data, the accuracy of the estimates of confounding due to the added variable(s), and the estimation of confidence intervals (although bootstrapping suggests itself).

Results: The method is shown to provide the correct unconfounded treatment effect estimate for several hypothetical scenarios. When applied to two published analyses supplying some, but not all, of the information needed, the method provides a qualitative indication of the general size and direction of residual confounding that is generally consistent with estimates of confounding suggested by comparisons to randomized trials.

Conclusions: This method may provide a new approach to estimating unconfounded treatment effects, including potentially when instrumental variables do not exist. Its performance, however, has not yet been validated. Research involving simulation and real-world data is needed, given the need for overall validation and to examine if specific uncertainties about aspects of the method affect its performance in certain situations.

999. A Method to Identify Patients Included within both the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN)

M Elle Saine,[1,2] Dena M Carbonari,[1,2] Craig W Newcomb,[1] Betina Blak,[3] Jason Roy,[1,2] Kevin Haynes,[1,2,4] Jennifer Wood,[5] Arlene M Gallagher,[6] Harshvinder Bhullar,[7] Serena Cardillo,[8] Sean Hennessy,[1,2] Brian L Strom,[1,2,9] Vincent Lo Re III.[1,2,8] *[1]Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [2]Center for Pharmacoepidemiology Research and Training, Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]AstraZeneca UK Limited, London, UK; [4]HealthCore, Inc., Wilmington, DE, USA; [5]Bristol-Myers Squibb, Hopewell, NJ, USA; [6]Clinical Practice Research Database, London, UK; [7]Cegedim Strategic Data Medical Research, London, UK; [8]Department of*

Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [9]Rutgers Biomedical & Health Sciences, Rutgers, the State University of New Jersey, Newark, NJ, USA.

Background: Investigators performing pharmacoepidemiologic research may seek to increase a study's size by utilizing data from the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN), two major UK electronic medical record databases. Prior studies have examined practice-level overlap between CPRD and THIN. However, methods to identify patient-level overlap have not been developed, and the proportion of patients included in both databases is unknown.

Objectives: To develop a method to identify patients included in both CPRD and THIN and to utilize this method to determine the proportion of type 2 diabetes mellitus (T2DM) patients who initiated oral anti-diabetic therapy with saxagliptin within both databases.

Methods: We conducted a cross-sectional study among T2DM patients initiating saxagliptin in CPRD and THIN from October 2009 to September 2012. Within both databases, we identified patients who were (1) ≥18 years, (2) newly prescribed saxagliptin, and (3) ≥180 days from enrollment. To identify patients included within both databases, we examined matches in demographic data (birth year, sex, patient registration date, family number, and marital status) and prescriptions (including dates) for the first two oral anti-diabetic drugs prescribed within the period of interest.

Results: We identified 4202 T2DM patients initiating saxagliptin in CPRD and 3641 in THIN who met inclusion criteria. A total of 2474 (59% of CPRD T2DM saxagliptin initiators; 68% of THIN T2DM saxagliptin initiators) patients were perfectly matched on all demographic data and both prescriptions. An additional 22 patients were matched on all demographic data but one of two prescriptions, and another 22 were matched on four of five demographic variables and both prescriptions, each representing 0.5% of CPRD T2DM saxagliptin initiators and 0.6% of THIN T2DM saxagliptin initiators.

Conclusions: Demographic and prescription data can identify patients in both CPRD and THIN. Among T2DM patients initiating saxagliptin, ≥60% were included within both CPRD and THIN.

1000. Concordance of Hospitalizations within the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) among Type 2 Diabetes Mellitus Patients

M Elle Saine,[1,2] Dena M Carbonari,[1,2] Craig W Newcomb,[1] Jason A Roy,[1,2] Kevin Haynes,[1,2,3] Jennifer Wood,[4] Arlene M Gallagher,[5] Serena Cardillo,[6] Sean Hennessy,[1,2] Brian L Strom,[1,2,7] Vincent Lo Re III.[1,2,6] *[1]Center for Clinical Epidemiology and Biostatistics, Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [2]Center for Pharmacoepidemiology Research and Training, Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [3]HealthCore, Inc., Wilmington, DE, USA; [4]Department of Global Pharmacovigilance and Epidemiology, Bristol-Myers Squibb, Hopewell, NJ, USA; [5]Clinical Practice Research Database, London, UK; [6]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [7]Rutgers Biomedical & Health Sciences, Rutgers, the State University of New Jersey, Newark, NJ, USA.*

Background: Pharmacoepidemiologic studies utilizing the Clinical Practice Research Datalink (CPRD) may seek to identify hospitalized events. CPRD can now be linked with Hospital Episode Statistics (HES) data among English patients, but the extent to which hospitalizations identified in CPRD are confirmed in HES, and vice versa, remains unknown.

Objectives: Among type 2 diabetes mellitus (T2DM) patients on oral anti-diabetic (OAD) drugs, we determined (1) the proportion of hospitalizations in CPRD that are confirmed in HES and (2) the proportion of hospitalizations identified in HES that are confirmed in CPRD.

Methods: We conducted a cross-sectional study among a sample of English T2DM patients initiating OAD therapy in CPRD from October 2009 to September 2012. We first identified an initial hospitalization/date in the CPRD database using a consultation or medical code and then determined if this hospitalization was recorded in HES data within ±30 days of the CPRD-recorded event. We then identified an initial hospitalization/date in the HES data based on an admission International Classification of Diseases 10th Revision diagnosis and then determined if the hospitalization was recorded in CPRD within ±30 days of the HES-recorded event.

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Results: Among 12 994 eligible OAD-treated English T2DM patients in CPRD, 5445 (42%) patients were identified with a hospitalization within CPRD. Of these, 3404 (63% [95%CI, 61–64%]) had the hospitalization confirmed by HES data within ±30 days. Among the same 12 994 patients, 5248 (40%) had a hospitalization identified in HES, of whom 2890 (55% [95%CI, 54–56%]) had the hospitalization recorded in CPRD within ±30 days.

Conclusions: Among a sample of OAD-treated English T2DM patients, 37% with a hospitalization in CPRD were not confirmed by HES, and 45% with a hospitalization in HES did not have the event recorded in CPRD. Pharmacoepidemiologic studies utilizing CPRD to identify hospitalized events should consider linkage with HES to ensure optimal identification of hospitalizations.

1001. Differential Use of Screening Mammography in Older Women Initiating Metformin or Sulfonylureas

Jin-Liern Hong,[1] Louise M Henderson,[2] Michele Jonsson Funk,[1] Jennifer L Lund,[1] Virginia Pate,[1] Til Stürmer.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Department of Radiology, University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC, USA.*

Background: A prior study found metformin (MET) initiators had more mammograms in 6 months pre-initiation than sulfonylurea (SU) initiators. Differential detection of breast cancer (BC) before and after initiation may distort the association between MET and BC.

Objectives: Examine receipt of screening mammography and risks of screen-detected BC in MET and SU initiators in 1 year pre-initiation and post-initiation.

Methods: We used 2006–2012 US Medicare claims to identify new users of MET or SU aged 65+ years at initiation, continuously enrolled in parts A/B for ≥2 years pre-initiation and 1 year post-initiation. We reported the frequency of mammograms and screen-detected BC in 1 year pre-initiation among all cohort members and in 1 year post-initiation among cancer-free cohort members. We also estimated the screening risk differences (RD) comparing MET to SU weighted by age, race, initiation year, and number of physician visits in the prior year.

Results: We identified 26 532 new users of MET and 9933 new users of SU; 35% of MET and 23% of SU had ≥1 mammogram in 1 year pre-initiation, a weighted RD of 7.1% (95%CI: 6.3 to 7.8). Mammography use decreased largely with age, increased with number of physician visits but remained similar across calendar year in MET and SU. The risk of incident screen-detected BC was 0.2% in MET and 0.1% in SU, with a weighted RD of 0.05% (95%CI: −0.02 to 0.12). Among cancer-free cohort members (MET: $N = 22\,973$; SU: $N = 8407$), MET was more likely to receive mammography than SU in 1 year post-initiation (weighted RD: 6.0%; 95%CI: 5.2 to 6.9). The risk of screen-detected BC was higher in MET (0.3%) than SU (0.1%), but the difference attenuated after weighting (weighted RD: 0.09%; 95%CI: −0.01 to 0.19).

Conclusions: Our results indicate differential screening mammography between MET and SU and slightly higher risks of screen-detected BC in MET than SU pre-initiation and post-initiation. Our study was limited by the small number of screen-detected BC cases. When interpreting the findings of MET on BC, researchers should consider the potential for more screenings pre-initiation and post-initiation which may decrease and increase cancer incidence, respectively.

1002. Determination of Proxies for Obesity Status in the Clinical Practice Research Database (CPRD)

Mona Cai,[1] Vinay Mehta,[2] Kimberly Brodovicz,[2] Cynthia Girman.[4] *[1]Epidemiology, University of North Carolina Chapel Hill Gillings School of Global Public Health, Chapel Hill, USA; [2]Pharmacoepidemiology, Merck and Co., Inc., North Wales, USA; [3]CERobs Consulting, LLC, Chapel Hill, NC, USA.*

Background: Electronic healthcare (EHR) databases are increasingly utilized for comparative safety and effectiveness research. However, these databases may not adequately capture information on key variables and comorbidities (e.g. obesity). Given the fact that obesity may confound the potential association between many exposures and outcomes, the identification of a proxy for obesity is critical for conducting pharmacoepidemiologic research using EHR data

Objectives: To identify a proxy for obesity which can be incorporated in future database studies

Methods: A general cohort of patients aged 25 years or older with at least 12 months continuous enrollment between 1997 and 2011 was selected from CPRD. Specific patient characteristics and comorbid conditions likely to be associated with obesity (i.e. BMI ≥ 30) were determined a priori and inputted into linear regression models to retrieve predicted BMI values. Data were divided into two equal sized datasets, one for determining predictors and another for testing predictors. A regression method was used to identify a set of proxies for obesity by comparing the iterative improvement between models with regard to their ability to classify patients into the correct BMI category. The association between obesity and subsequent type 2 diabetes (T2DM) and the association between the proxies and T2DM were tested in a cohort where equal numbers of cases and controls were selected and compared using the c-statistic.

Results: A total of 612 450 patients were identified, including 38.2% of patients who were obese and 50.1% who had a diagnosis for T2DM. The final set of proxies included systolic blood pressure, gender, retinopathy, and depression. The models with obesity status, BMI (as a continuous variable), and the set of obesity proxies yielded c-statistics of 0.661, 0.742, and 0.722, respectively

Conclusions: Results from this study suggest that a set of proxy variables for obesity could not be determined in CPRD. Important variables associated with obesity may not be adequately captured in CPRD. Future studies using CPRD should consider directly adjusting for BMI or obesity status in circumstances where obesity is an important potential comorbidity

1003. Application of the International Society on Thrombosis and Haemostasis (ISTH) Definition of Major Bleeds to Bleeding Events within a Post-Authorization Safety Study

Miranda Davies,[1,2] Vicki Osborne,[1,2] Deborah Layton,[1,2] Saad Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, UK; [2]University of Portsmouth, Portsmouth, UK.*

Background: Haemorrhage is a frequent complication of anticoagulant (AC) use. In order to compare incidences between trials a definition of major bleeds (MB) in non surgical studies was developed by the International Society on Thrombosis and Haemostasis (ISTH) in 2005. In recent years, the Committee for Medicinal Products for Human Use (CHMP) has recommended its use in studies for prevention of stroke and systemic embolic events (SEE) in patients (pts) with non-valvular atrial fibrillation (NVAF) and prevention of deep vein thrombosis (DVT) and pulmonary embolus (PE). Bleeds reported in a Specialist Cohort Event Monitoring (SCEM) study on the oral AC rivaroxaban (conducted as part of risk management plan) will be classified using this definition.

Objectives: To describe the methodological considerations of applying this definition to observational data.

Methods: Aim to collect data on 1700 pts treated for the prevention of SEE [$n = 561$], and the treatment and prevention of recurrent DVT and PE [$n = 1005$]. Recruitment was on September 2013–2016. Information (info) was obtained on bleeds that occurred during initial 12 weeks; criteria for MB included: a fall in Hb of ≥2 g/dL, a transfusion of ≥2 units, critical organ site or fatal outcome. Bleeds will be classified as clinically relevant non-major (CRNM) if none of the MB criteria were met, but if medical attention was required and/or a change in antithrombotic therapy and/or any other bleed with clinical consequences.

Results: To minimise misclassification, supplementary info will be used to validate and confirm the type, obtain missing data and further details of the bleed (site, management and outcome). All bleeds will be adjudicated by an expert, and interim results will be published.

Conclusions: By systematically applying the ISTH definition, we hope to gain better understanding of the type of bleeds reported in a cohort of AC users, associated risk factors and outcome details. This should enable more meaningful comparisons to be made between major and CRNM bleeding incidences obtained in this setting with those observed during trials

1004. Validity Assessment of Rosuvastatin Prescribing Data from Electronic Health Records (EHR) in the United States

Christopher G Rowan,[1] Nikita Stempniewicz,[1] James Flory,[2] Tobias Gerhard,[3] James D Lewis,[4] John Cuddeback,[1] Sean Hennessy.[4] *[1]American Medical Group Association, Alexandria, VA, USA; [2]Weill-Cornell School of Medicine, New York, NY, USA; [3]Ernest Mario School of Pharmacy, Piscataway, NJ, USA; [4]University of Pennsylvania, Philadelphia, PA, USA.*

Background: Electronic health records (EHRs) permit observational research with clinical and laboratory data more granular than administrative claims data. However, the relationship between EHR prescribing (Rx) data and the pharmacy claims traditionally used to classify longitudinal medication exposure has not been studied.

Objectives: To assess the validity (sensitivity, specificity, PPV, and NPV) of classifying rosuvastatin exposure using EHR Rx data compared to pharmacy claims data.

Methods: The study population was extracted from the Optum Labs Data Warehouse (OLDW), which contains de-identified administrative claims and EHR data. We included patients who had both (linked) claims (with a pharmacy benefit) and EHR data in 2012. We compared ambulatory rosuvastatin EHR Rxs with pharmacy claims for rosuvastatin in 1-, 3-, 6-, and 12-month periods. We classified rosuvastatin exposure by ≥1 Rx in EHR data and by ≥1 pharmacy claim. We stratified this analysis by patients with an incident versus prevalent EHR Rx for rosuvastatin.

Results: A total of 215 634 patients were included in the 12-month period. A total of 4887 patients had ≥1 rosuvastatin EHR Rx during the period, and 5976 had ≥1 claim for rosuvastatin. Among patients with an EHR Rx, approximately 65% of patients had an EHR Rx for rosuvastatin in the prior year (prevalent cohort). Patients with a prevalent rosuvastatin EHR Rx were 15% more likely to have a pharmacy claim than those with an incident EHR Rx. The sensitivity (of EHR Rx compared to pharmacy claims) in the 1-, 3-, 6-, and 12-month periods was 36%, 42%, 54%, and 68%, respectively. The specificity was 100%, 100%, 100%, and 100%. The PPV was 66%, 80%, 83%, and 83%. The NPV was 99% 99%, 99%, and 99%. For all exposure periods, patients with an incident rosuvastatin EHR Rx had lower sensitivity and PPV, and higher specificity and NPV, than patients with a prevalent EHR Rx.

Conclusions: For rosuvastatin, PPV (probability of having a pharmacy claim among patients with an EHR Rx) increases with the time interval, but it stabilizes around 80% at 3 months and remains at that level through 12 months. In order to increase the validity of classifying rosuvastatin exposure using EHR Rx data, researchers should include at least a 3-month period.

1005. Validation of Colorectal Cancer Diagnoses in the Health Improvement Network in the United Kingdom

Montse Soriano-Gabarró,[1] Lucía Cea Soriano,[2] Luis A García Rodríguez.[2] *[1]Bayer Pharma AG, Berlin, Germany; [2]Spanish Centre for Pharmacoepidemiologic Research, Madrid, Spain; [3]Spanish Centre for Pharmacoepidemiologic Research, Madrid, Spain.*

Background: Confirmation of study outcomes recorded in healthcare databases is important to assess the validity and completeness of the coding system.

Objectives: To validate the recorded diagnoses of colorectal cancer (CRC) and identify false negatives in The Health Improvement Network (THIN) UK primary care database.

Methods: We conducted a validation study of cases of incident CRC among patients aged 40–90 years between 2000 and 2011. The CRC diagnoses entered in THIN via Read codes ($N=3805$) were confirmed by (i) manual review of patients' electronic medical records (EMRs) including free-text comments, (ii) questionnaires sent to primary care practitioners (PCPs; for a random sample of 100 potential CRC cases), and (iii) Hospital Episode Statistics (HES) data among linked practices. In addition, false negatives in THIN (cases unrecorded in THIN) were identified by searching for International Classification of Diseases (ICD) codes related to CRC in HES data.

Results: Of 3805 CRC cases identified in THIN based on Read codes, 3033 patients (80.0%) were confirmed as definite cases after manual review of patients EMRs. The confirmation rate was 86.0% after removing patients identified from THIN via a Read code for 'fast track referral for suspected CRC'. The response rate from PCPs was 87.0% ($n=87$). Among patients classed as CRC cases after manual review of EMRs ($n=71$), all were confirmed by PCPs as cases (100% concordance). Among the 3805 patients, we linked 728 patients to HES data (568 patients had been confirmed as cases and 160 as non-cases in THIN following manual review). A total of 89.6% of confirmed cases in THIN were also confirmed in HES. Of 160 linked patients that were classed as non-cases in THIN after manual review, four were identified as cases in HES (2.5%). Finally, in the subgroup of THIN practices linked to HES, we found a total of 32 CRC cases identified only in HES representing an additional 5.3% (32/604) of cases missed when using only THIN (false negatives).

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Conclusions: Our results show a high confirmation rate of CRC diagnoses in THIN after a thorough review of clinical information in EMRs and also a low false negative rate.

1006. Withdrawn by author

1007. Medical Record Validation of Algorithms for Acute Myocardial Infarction (AMI) within a United States (US) Administrative Claims Database

Kathleen M Mortimer,[1] Stephen M Ezzy,[1] Jillian T Jessup,[1] Robert V Gately,[1] John D Seeger.[1,2] *[1]Epidemiology, Optum, Waltham, MA, USA; [2]Brigham and Women's Hospital, Boston, MA, USA.*

Background: Pharmacoepidemiology research based on claims-based algorithms is enhanced by validation studies to assess performance metrics of the algorithms given that algorithm performance may vary when applied to different patient populations.

Objectives: To re-evaluate and, if necessary, revise previously published claims-based algorithms for AMI, based on comparison to adjudicated medical record review.

Methods: A retrospective cohort study in administrative claims data among patients (age ≥18 years) with dispensings for antimuscarinic medication for the treatment of overactive bladder included physician adjudication of medical records to validate an AMI algorithm (01 Jan 2004 to 30 Sep 2012). We published algorithm (1+ claims with an ICD-9 code of 410.xx in the primary or secondary position on an emergency department or inpatient claim) was implemented, a lower than previously reported positive predictive value (PPV) was found. Revised algorithms incorporating diagnosis related groups (DRG), death and revascularization codes were explored.

Results: Among 25 charts obtained based on the published algorithm, there were 16 confirmed cases, six non-cases and three questionable cases (PPV of 64%, 95%CI: 43%, 82%). The revised algorithm was: (a) 1 + claims with AMI diagnosis code and (death or revascularization) or (b) 2+ claims with AMI codes or (c) 1 + claims with an AMI DRG. Among the patients who met the new claims-based case definition ($n = 16$), the PPV was 100%.

Conclusions: Claims-based algorithms may not perform similarly in all populations and revisions to published algorithms may increase PPVs. This expanded algorithm provides a high PPV, allowing for timely estimation of AMI incidence based on claims that is in close agreement with estimates based on medical record review.

1008. Validation of Diagnosis and Treatment Codes for Patients with Acute Lymphoblastic Leukemia (ALL) in Denmark

Victoria M Chia,[1] Alma B Pedersen,[2] Thomas B Rasmussen,[2] Aaron J Katz,[1] Michael A Kelsh,[1] Sally Wetten,[3] Mette Norgaard.[2] *[1]Center for Observational Research, Amgen Inc, Thousand Oaks, CA, USA; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Centre for Observational Research, Amgen Ltd, Uxbridge, UK.*

Background: In Denmark, patients with acute lymphoblastic leukemia (ALL) may be identified using diagnosis codes in the Danish administrative records. The validity of these codes is not currently known but is critical for understanding how to identify patients with ALL for pharmacoepidemiology studies.

Objectives: To evaluate the validity of diagnosis codes for identifying ALL patients and treatment codes to assess patterns of care for ALL patients in Danish administrative databases.

Methods: We collected data from the Danish Cancer Registry (DCR), the Danish National Registry of Patients (DNRP), and medical records. We identified patients with ALL based on the ICD-10 code DC91.0. Data on treatment [chemotherapy (CT), stem cell transplantation (SCT), radiation therapy (RT), and palliative care] after ALL diagnosis date were collected from the DNRP. To validate these codes, we reviewed the medical records for 182 patients diagnosed with ALL from 1998–2009 in the DCR. These patients represented all eight hematological departments, including three pediatric departments, in Denmark where treatment for ALL occurs. Only records from the hospital where the patients received their ALL-specific treatments were reviewed. Positive predictive values (PPV) and negative predictive values (NPV) were calculated for the ALL diagnosis code from the DCR, as well as treatments collected from the DNRP.

Results: Among the 182 medical records reviewed, an ALL diagnosis from the DCR was verified in 179 patients, for a PPV of 98.4% (95%CI 95.7%, 99.5%). Approximately 93% of patients were identified as having received treatment by the DNRP, with 92.7% receiving CT, 11.2% receiving SCT, and 9.5% receiving RT. PPVs for chemotherapy, SCT and RT were 94.0% (95%CI 89.6%, 96.9%), 75.0% (95% CI53.6%, 89.8%), and 41.2% (95%CI 20.7%, 64.4%), respectively. NPVs for treatments ranged from 38.5% (for chemotherapy) to 98.8% (for RT).

Conclusions: The ICD-10 diagnosis code for ALL has high validity in Danish administrative databases; however, careful consideration is required when using administrative data for properly identifying treatments.

1009. Revisions to Published Algorithms for Stroke within a United States (US) Administrative Claims Database

Kathleen M Mortimer,[1] Stephen M Ezzy,[1] Jillian T Jessup,[1] Robert V Gately,[1] John D Seeger.[1,2] *[1]Epidemiology, Optum, Waltham, MA, USA; [2]Brigham and Women's Hospital, Boston, MA, USA.*

Background: Claims-based outcome algorithms may need updating as medical and coding practices change.

Objectives: To re-evaluate and, if necessary, revise a published claims-based algorithm for stroke through medical record review and adjudication.

Methods: A retrospective cohort study within administrative claims data among adults with dispensings for antimuscarinic medications for the treatment of overactive bladder included medical chart adjudication for validation of a stroke algorithm (01 Jan 2004 to 30 Sep 2012). An established algorithm (1+ inpatient or emergency department claims with ICD-9 diagnosis code 430, 431, 433.x1, 434.x1 or 436, first position only) had published positive predictive values (PPV) >90%. Among study patients for whom the medical record contained sufficient information for adjudication, PPVs were estimated (number of adjudicator-confirmed cases/number of algorithm-identified cases). Revised algorithms including diagnosis-related groups (DRG), and codes for medical imaging, therapies or equipment. PPVs were re-estimated using the subset of adjudicated charts for patients who met the new algorithm case criteria.

Results: Initially, 31 of 94 claims-identified cases with charts were confirmed through medical record review (PPV 33%). The PPV among patients with only code 436 was 0%. This code description changed from *Cerebrovascular accident* to *Acute, but ill-defined, cerebrovascular disease* in 2006, and cases identified subsequently were inaccurately identified as strokes. Our revised algorithm required (a) 1+ claims with an ischemic code (433.x1, 434.x1) or (b) 1+ claims with hemorrhagic code (430, 431, without head injury) or (c) DRG for stroke. The definition also required 1+ codes for medical imaging, post-stroke physical or occupational therapies or equipment, anticoagulant medical therapy or death. The revised algorithm classified 21 of 32 algorithm-identified cases with charts as confirmed cases (PPV 66%).

Conclusions: Updating of codes included in published algorithms is essential for accurate case definition. Inclusion of post-stroke imaging, therapies and equipment also improved algorithm performance slightly.

1010. Sensitivity of Diagnosis and Treatment Codes in the Identification of Adults with Acute Lymphoblastic Leukemia in SEER-Medicare

Aaron J Katz,[1] Victoria M Chia,[1] Mark D Danese,[2] Jennifer Duryea,[2] Michael A Kelsh,[1] Deborah P Lubeck.[2] *[1]Center for Observational Research, Amgen Inc., Thousand Oaks, CA, USA; [2]Outcomes Insights, Inc., Westlake Village, CA, USA.*

Background: Diagnosis and treatment codes may be useful in identifying patients with acute lymphoblastic leukemia (ALL) in large administrative databases. However, how these codes perform in detecting patients with ALL is not well known.

Objectives: To evaluate the sensitivity of diagnosis and treatment codes from administrative data in selecting adult ALL patients in the SEER-Medicare database.

Methods: Within the SEER-Medicare linked database, we selected patients aged ≥18 years with a confirmed diagnosis of ALL in SEER between 2000 and 2010. We excluded patients without Medicare parts A and B coverage 3 months prior to and ≥30 days post SEER diagnosis of ALL. We randomly split patients into exploratory and test groups. In the exploratory group, we evaluated the sensitivity of diagnosis and chemotherapy administration codes within Medicare

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inpatient and physician claims against the diagnosis of ALL in SEER data to inform the development of algorithms for detecting ALL patients. The performance of developed algorithms will be assessed among test group patients in subsequent analyses.

Results: We identified 850 patients with an ALL diagnosis in SEER. Of the 817 meeting inclusion criteria, 670 (82.0%) were aged 65 years or older. Among the 408 patients randomized to the exploratory analysis group, 334 (81.9%) had at least one hospitalization with an ALL diagnosis at discharge and no diagnosis codes for other malignancies; of these 334 patients, only 152 (45.5%) had a hospitalization indicative of induction chemotherapy administration. At least one physician claim with a diagnosis of ALL was present for 376 (92.2%) patients, including 365 (89.5%) with ALL as the primary diagnosis. Only 294 (72.1%) patients had two physician claims with an ALL diagnosis at least 30 days apart.

Conclusions: Diagnosis codes within physician claims have higher sensitivity for identifying adult ALL patients than codes in hospitalization claims; chemotherapy codes may have limited utility in identifying de novo ALL in administrative claims data, particularly among older adults.

1011. Small Differences among Approaches in the Estimated Prevalence of a Very Rare Disease

Dana Y Teltsch,[1] Richard Scott Swain,[1] Don Robinson Jr.,[2] Matthew W Reynolds.[1] *[1]Evidera, Lexington, MA, USA; [2]Janssen, Raritan, NJ, USA.*

Background: Prevalence estimation of very rare diseases (less than 1 in 100 000 of the general population) is challenging as patients are commonly identified from specialized referral centers with no clear referral area or base population. With small number of cases, small variations in patient inclusion and definitions of relevant base population may result in substantial differences in estimates of disease prevalence.

Objectives: Compare several established approaches for the estimation of prevalence of rare diseases.

Methods: The patient series consisted of Multicentric Castleman's Disease (MCD) patients seen in one or two specialized treatment centers. The size of the reference population (age 18 years and older) was based on the 2000 CENSUS data, patient 3-digit ZIP (postal) code areas, and several alternative approaches to the inclusion of ZIP areas in the base population. These approaches consisted of: spatial clusters based approach using hotspots analysis; 4 hours driving distance based area; and a geographical state-based referral region.

Results: The number of MCD patients included in the ZIP code area that was considered to contribute the cases ranged from 14 to 19 depending on approach: (19 clusters-based cases; 14 driving distance-based cases; and 14 state-based cases). The prevalence estimation based on cases from one center ranged from 2.4 to 2.7 per million population (2.5 cluster-based; 2.4 driving distance-based; and 2.7 regional-based). The addition of data from a second national referral center to the state-based prevalence estimate resulted in the addition of two patients (to a total of 16) and a prevalence estimate of 3.1 per million population.

Conclusions: Prevalence proportion estimates by the different approaches were similar. In lack of a comparison, it is not known which of the estimates is the most accurate. The optimal estimation approach will depend on disease and center-specific characteristics.

1012. Implications for Signal Detection of Duplicated Case Reports of Stress Cardiomyopathy

Manfred Hauben,[1] Maribel Salas,[2,3] Peter Huber,[1] Eric Hung.[1] *[1]Worldwide Safety and Regulatory, Pfizer Inc, New York, NY, USA; [2]Worldwide Safety and Regulatory, Pfizer Inc, Collegeville, PA, USA; [3]Clinical Safety & Risk Management, Merck Research Laboratories, Upper Gwynedd, PA, USA.*

Background: Duplicated case reports can be an important issue in safety signal detection. The potential impact (e.g. false positive and negative findings) can be 'extreme' despite the use of duplicate detection algorithms in proprietary software.

Objectives: We describe an example of 'extreme duplication' in the US FDAERs database that was discovered during routine signal evaluation activities. Specifically, we identified numerous duplicated case reports of stress cardiomyopathy (Tako Tsubo cardiomyopathy) when assessing a drug-event combination (DEC).

Methods: The US FAERS database was searched for all reported adverse events encoding to MedDRA

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(version 16.0) Preferred Terms (PT) stress cardiomyopathy received through 27 August 2012, which were obtained via Freedom of Information (FOI). For each case, we extracted: event (date, PT, SOC), case (ISR number, age, gender, seriousness and country), medication (generic name, trade name, indication, start and end date, dose, route of administration, manufacturer, lot, dechallenge and rechallenge), outcome (recovered, death, life threatening, hospitalization, required intervention, disability and other), source (health professional, consumer, literature, clinical study, regulatory agency, foreign, other) and case narratives. Duplicated reports were identified manually and complemented by statistical analysis, and visualization of variables distribution pertinent to duplicate detection. The impact of duplication on disproportionality analysis (DA) was assessed.

Results: There were 40 stress cardiomyopathy cases. After detailed manual review and statistical analysis, more than 60% of the cases were considered be duplicated. Characteristics of spontaneous reports that predispose to extreme duplication will be discussed. Potential impact of this level of duplicate reporting on measures of disproportionate reporting are significant.

Conclusions: Duplicate reporting can impact signal detection, depending on various factors. Investigators should look for potential duplicates. Univariate and multivariate statistical analysis can support duplicate detection by helping to visualize patterns of relevant variables.

1013. Differential Racial and Regional Effects of Baseline Timeframe on Potential Bias in Risk Factor Assessment Using EHR Data

Anne Yuk-Lam Ho,[1] Jason L Vassy,[1,2] David R Gagnon,[1,3] J Michael Gaziano,[1,2] Jacqueline Honerlaw,[1] Sanjay Raju,[1] Peter WF Wilson,[1,4] Kelly Cho.[1,2] *[1]Massachusetts Veterans Epidemiology Research and Information Center, Boston VA Healthcare System, Boston, MA, USA; [2]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Department of Biostatistics, School of Public Health, Boston University, Boston, MA, USA; [4]Clnical Cardiovascular Research Institute, Emory University, Atlanta, GA, USA.*

Background: There are over 15 years of electronic health records (EHR) representing over 20 million patients within the US VA Healthcare System. Such database allows for large-scale epidemiological investigations. However, with the underlying heterogeneity by race and utilization patterns, there exists potential selection bias when defining the timeframe of baseline risk factor assessment.

Objectives: Using a large-scale cardiovascular disease (CVD) cohort, we investigated the impact of race and region on potential for bias when defining the baseline timeframe for CVD risk factors.

Methods: We identified 589 361 eligible patients between 2000 and 2007 from the New England (VISN1) and Southeast (VISN7) regions and stratified by self-identified Whites and African Americans. We anchored the index date to first eligible lipid results date, and then expanded the baseline timeframe by 1-week interval before or after, assessing the proportion of eligible patients with blood pressure (BP) results in each successive interval. We compared three mutually exclusive groups: (1) those with BP on the index date, (2) those with BP within the 90th percentile to either side of the index date, and (3) those with no BP within the 90th percentile. We further compared their baseline CVD, diabetes, mental health conditions, aspirin use, and drive time to facility.

Results: Group1 contained 146 636 (61%) and 289 906 (83%) of the eligible patients in VISN1 and VISN7, respectively. This proportion reached 90% within +91 or −154 days from the index date in VISN1 and only +7 or −14 days in VISN7. Group3 had lower prevalence of baseline comorbidities, and fewer outpatient visits. Compared to Whites, African Americans had more frequent outpatient contacts, lower prevalence in baseline CVD but higher prevalence in mental health conditions.

Conclusions: To minimize selection bias when creating a prospective CVD EHR cohort, data on patients with low utilization pattern requires special handling. The potential for bias may vary considerably across different regions and between Whites and African Americans within the same large integrated health system.

1014. Developing a Stroke Severity Index Based on Administrative Data Was Feasible Using Data Mining Techniques

Cheng-Yang Hsieh,[1,2] Sheng-Feng Sung,[3] Yea-Huei Kao Yang,[2] Huey-Juan Lin,[4] Chih-Hung Chen,[5]

Yu-Wei Chen,[6] Ya-Han Hu.[7] *[1]Department of Neurology, Tainan Sin Lau Hospital, Tainan, Taiwan; [2]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [3]Division of Neurology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan; [4]Department of Neurology, Chi Mei Medical Center, Tainan, Taiwan; [5]Department of Neurology, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [6]Department of Neurology, Landseed Hospital, Taoyuan, Taiwan; [7]Department of Information Management, Institute of Healthcare Information Management, National Chung Cheng University, Chiayi, Taiwan.*

Background: Case-mix adjustment is difficult for stroke outcome studies using administrative data. However, relevant prescription, laboratory, procedure, and service claims might be surrogates for stroke severity.

Objectives: This study proposes a method for developing a stroke severity index (SSI) by using administrative data.

Methods: We identified 3577 patients with acute ischemic stroke from a hospital-based registry and analyzed claims data with plenty of features. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). We used two data mining methods and conventional multiple linear regression to develop prediction models, comparing the model performance according to the Pearson correlation coefficient between the SSI and the NIHSS. We validated these models in four independent cohorts by using hospital-based registry data linked to a nationwide administrative database.

Results: We identified seven predictive features and developed three models. The k-nearest neighbor model (correlation coefficient, 0.743; 95% confidence interval, 0.737–0.749) performed slightly better than the multiple linear regression model (0.742; 0.736–0.747), followed by the regression tree model (0.737; 0.731–0.742). In the validation cohorts, the correlation coefficients were between 0.677 and 0.725 for all three models.

Conclusions: The Claims-Based SSI enables adjusting for disease severity in stroke studies using administrative data.

1015. Strategies to Handle Missing Information in Predictive Modelling Using Routinely Collected Data: Differences in Identified Predictors and Model Performance

Albert Roso,[1] Irene Petersen,[2] Gary Collins,[3] Montse Rué,[4] Cristian Tebé,[5,6] Mireia Espallargues,[5] Daniel Prieto-Alhambra,[1,3] PRESS-UP Research Group.[1,5] *[1]SIDIAP Database, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain; [2]Primary Care and Population Health, University College London (UCL), London, UK; [3]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK; [4]Ciencies Mediques Basiques, IRBLLEIDA, Universitat de Lleida, Lleida, Catalonia, Spain; [5]Registre Català d'Artroplàsties (RACat), Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Generalitat de Catalunya, Barcelona, Catalonia, Spain; [6]Statistical Advisory Service, Bellvitge Biomedical Research Institute-IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Catalonia, Spain.*

Background: The use of routinely collected data to develop predictive tools (PT) has grown in recent years. Missing information can affect selection of key predictors and lead to inaccurate estimation of model coefficients.

Objectives: We aimed to compare different methods for handling missing data in routinely collected electronic health care records for PT modelling.

Methods: Setting and participants: Data from primary care and pharmacy dispensations (SIDIAP) were linked to RACat, which collects information for patients undergoing total hip arthroplasty (THA) in Catalonia (Spain). Individuals aged ≥40 years undergoing THA in the period June 2005 to 2012 in the linked dataset were included. Patients with previous hip fracture or malignancy were excluded.

Outcome: 1-year all-cause mortality.

Potential predictors: age, sex, body mass index, smoking, alcohol drinking, Charlson co-morbidity index, healthcare resource use, implant type, hospital volume, drugs used in the previous year, and indication.

Statistics: Backwards logistic regression using backwards elimination ($p = 0.1$) was used to identify key predictors in the PT. Discrimination of the PT was assessed by calculating the area under the ROC curve and agreement between observed, and predicted risk was assessed graphically by a calibration plot.

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Complete case analysis (CC) and multiple imputation with 10 imputed datasets (MI) were compared in terms of variable selection, coefficients, and PT performance. Body mass index, smoking, and alcohol drinking were imputed using both study outcome and potential predictors.

Results: Among 11 427 subjects, 4717(41.3%) had complete data. Poor variable selection and biased coefficients were obtained for CC analysis compared to MI. Conversely, good discrimination and calibration were obtained for both methods as seen in ROC curve and observed/expected plots.

Conclusions: Common strategies to handle missing information were compared. Loss of key predictors and related bias was found for CC analysis. MI must be used to account for missing information in predictive modelling using routinely collected data.

1016. Medical Record Validation of Algorithms for Ten Types of Cancer within a United States (US) Administrative Claims Database

Kathleen M Mortimer,[1] Stephen M Ezzy,[1] Jillian T Jessup,[1] Robert V Gately,[1] John D Seeger.[1,2] [1]*Epidemiology, Optum, Waltham, MA, USA;* [2]*Brigham and Women's Hospital, Boston, MA, USA.*

Background: Claims-based algorithms may misclassify patients as cases who have claims associated with diagnostic work-ups where the diagnosis is ultimately ruled out. Validation of such algorithms through medical record review provides performance metrics such as positive predictive values (PPV). High PPVs are necessary for accurate estimation of study outcomes.

Objectives: To validate algorithm-based cancer diagnoses through comparison to physician-adjudicated medical record review (specific cancers: bladder, colon/rectum, kidney and renal pelvis, lung and bronchus, melanoma, non-Hodgkin's lymphoma, pancreas, prostate, breast and uterus).

Methods: A retrospective cohort study within administrative claims data among patients (age ≥18 years) with dispensings for antimuscarinic medications for the treatment of overactive bladder (OAB) included physician adjudication of medical records for validation of case status for 10 types of cancer (01 January 2004 to 30 September 2012). Each algorithm required 2+ claims for the type-specific cancer at least 30 days but not more than 90 days apart. PPVs were estimated (the number of adjudicator-confirmed cases/the number of algorithm-identified cases) among patients for whom the medical record contained sufficient information for adjudication.

Results: Approximately 30 charts for each of the ten cancers were obtained. The PPVs ranged from 100% for breast cancer (women only, $n=31$) to 80% (95% CI: 68–94%) for lung cancer (both genders combined, $n=36$). The composite PPV for all 10 types of cancer was 91% (95%CI: 87–94%, $n=305$). Stratification by baseline history of cancer did not substantially alter the results.

Conclusions: The pre-specified claims-based cancer algorithms accurately identified cancer cases with a high PPV for the composite cancer outcome as well as for each individual cancer type.

1017. Assessment of Residual Confounding and Selection Bias in Studies of Anti-Diabetes Medications

Ayad K Ali,[1] Stephen P Motsko,[1] Jonathan L Swain.[1] [1]*Global Patient Safety, Eli Lilly and Company, Indianapolis, IN, USA.*

Background: Given stepwise pharmacologic therapy of diabetes, residual confounding due to selection bias in studies of anti-diabetes medications (ADM) is likely for outcomes that are linked to diabetes severity.

Objectives: This real-world study assessed residual confounding attributed by selection bias among ADM classes when studying the distribution of major cardiovascular events (MACE) before exposure to ADM.

Methods: Patients with type 2 diabetes who were enrolled in a nationally representative healthcare insurance database between 2006 and 2011 and who initiated ADM were included in this cohort study. ADM included metformin; sulfonylureas; thiazolidinediones (TZD); incretin enhancers (incretins); and insulin. The outcome of interest was the incidence of hospital-related non-fatal MACE during 12 months pre-ADM initiation after accounting for confounding factors during the baseline period of 12 months preceeding the outcome measurement period. These factors included demographics, diabetes severity and duration, comorbidities, co-medications, laboratory tests, and healthcare utilization indices. Proportional hazards regression was used to calculate pre-exposure

MACE hazard ratios (HR) between ADM exposure groups.

Results: Baseline characteristics of 479 099 ADM initiators were studied (mean age 58.3 years, SD = 11.8), corresponding to 38% metformin, 22% sulfonylureas, 10% TZD, 13% incretins, and 17% insulin initiators. There were significant differences in baseline characteristics between ADM groups, especially in diabetes severity and complications. Adjustment for these characteristics did not remove baseline differences between ADM groups and yielded pre-exposure MACE HR beyond the null: Compared to metformin (sulfonylureas, HR = 2.43; TZD, HR = 1.96; incretins, HR = 1.38; insulin, HR = 1.85); compared to sulfonylureas (TZD, HR = 0.81; incretins, HR = 0.57; insulin, HR = 0.76); compared to TZD (incretins, HR = 0.70; insulin, HR = 0.94); and insulin compared to incretins, HR = 1.34.

Conclusions: The findings suggest the presence of residual confounding in studies of ADM despite adjustment, and diabetes severity and complications should be taken into account when selecting comparison groups.

1018. The Impact of Time-Window Bias on the Assessment of Long-Term Effect of Medication Adherence: The Case of Secondary Prevention after Myocardial Infarction

Mirko Di Martino,[1] Ursula Kirchmayer,[1] Nera Agabiti,[1] Lisa Bauleo,[1] Danilo Fusco,[1] Carlo Alberto Perucci,[2] Marina Davoli.[1] *[1]Department of Epidemiology, Regional Health Service, Lazio Region, Rome, Italy; [2]Senior Epidemiologist Consultant, Rome, Italy.*

Background: Time-window bias was described in case–control studies that analyzed a dichotomous exposure and reported an overestimation of drug benefit. No studies measured the impact of this bias on the assessment of the effect of medication adherence on health outcomes.

Objectives: Our goals were to estimate the association between adherence to drug therapies after myocardial infarction (MI) and the incidence of a new MI, and to quantify the error that would have been produced by a time-window bias.

Methods: Patients discharged after MI in 2006–2007 were enrolled and followed through 2009. A nested case–control study was performed. Controls were selected using both time-dependent sampling and the "biased" time-independent sampling. Adherence to antiplatelets, beta-blockers, ACEI/ARBs and statins was calculated using the proportion of days covered (PDC).

Results: A total of 6880 patients were enrolled. Using time-dependent sampling, a protective effect was detected for all study drugs. Using time-independent sampling, the beneficial effect was attenuated, as in the case of antiplatelet agents and statins, or completely masked, as in the case of ACEI/ARBs and beta-blockers. For ACEI/ARBs, the time-dependent approach produced odds ratios versus "$0 < \text{PDC} \leq 0.5$" of 0.83 (95%CI: 0.57–1.21) and 0.72 (0.55–0.95) for "$0.5 < \text{PDC} \leq 0.75$" and "$\text{PDC} > 0.75$", respectively. Using the time-independent approach, the odds ratios were 0.96 (0.65–1.43) and 1.00 (0.76–1.33), respectively.

Conclusions: When the exposure is adherence to chronic medication, measured during a lengthy observation period that begins with an acute and traumatic event, the selection of controls using time-independent sampling may underestimate any beneficial adherence effect. In both the cohort and case–control study designs, the probability of a time-dependent exposure changes with the length of follow-up. Therefore, time-independent exposure definitions will introduce a bias when the duration of follow-up varies with the outcome. The persistence of time-related biases in peer-reviewed publications suggests the need for increased awareness of this methodological pitfall.

1019. Does the Length of the "Pre-Exposure" Window Affect the Relative Risk Estimate? A Self-Controlled Case Series Study

Gema Requena,[1,2] Francisco J De Abajo,[1,3] Consuelo Huerta,[4] Stephen J Evans,[5] Ian J Douglas.[5] *[1]Unit of Pharmacology, Department of Biomedical Sciences, School of Medicine, University of Alcalá, Madrid, Spain; [2]Global Epidemiology Department, OXON Epidemiology, London, UK; [3]Clinical Pharmacology Unit, University Hospital Príncipe de Asturias, Madrid, Spain; [4]BIFAP Research Unit, Spanish Agency of Medicines and Medical devices, Madrid, Spain; [5]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK.*

Background: One of the assumptions required by the self-controlled case series (SCCS) method is that the

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occurrence of an event must not alter the probability of subsequent exposure.

Objectives: We aimed to test the potential event-exposure dependence examining how the length of the "pre-exposure" window affects the relative risk estimate of hip/femur fractures (HFF) with the use of benzodiazepines (BZD) as a case study and investigating the risk in such windows if any.

Methods: A SCCS method was applied in patients with a diagnosis of HFF registered in BIFAP (Spanish primary care database) and who were free of HFF 12 months and free of BZD exposure 6 months before the start date. Exposure to BZD was divided into baseline (non-use), current use (up to 30 days after the end of last supply) and recent use (1–60 days after current use). The relative risks of current use (IRR; 95%CI) as compared to baseline were estimated using a conditional Poisson regression analysis adjusted by age. First, pre-exposure windows of 15, 30, and 60 days were separated from baseline time. Secondly, baseline time before exposure was divided in periods of 7 days, and we excluded them from baseline in a stepwise manner until no increased risk was found.

Results: The IRR for HFF associated with current use of BZD was 0.79 (0.72–0.86). Excluding a 15-day pre-exposure window from baseline, the IRR during current use raised to 1.29 (1.18–1.41); with 30-day window, 1.43 (1.31–1.57) and with 60-day window, 1.56 (1.42–1.72). Finally, the IRR reached a plateau (1.64; 1.48–1.81) after a period of 182 days of pre-exposure was excluded from baseline.

Conclusions: In case of a plausible event-exposure dependence, as the administration of an anxiolytic or sedative after a traumatic intervention, the risk in the reference category must be always explored, since otherwise results may be biased.

1020. The Critical Impact of Complex Cases Behavior on the Performance of Self-Controlled Case Series Method

Ling Zhang, Jasmanda Wu, Juhaeri Juhaeri.
Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, USA.

Background: In the previous study, we used a self-controlled case series (SCCS) in examing the association between tricyclic antidepressant (TCA) and acute myocardial infarction (AMI) in the Clinformatics Data Mart (United HealthCare, formerly LabRx) database and OSIM2, to compare analytical method performance. It showed almost opposite results between these two databases. Rate ratio (RR) of AMI risk is 1.20 (95%CI 1.01–1.42) in Clinformatics Data Mart and 0.87 (95%CI 0.80–0.95) in OSIM2.

Objectives: The objective is to find out why the results are so different.

Methods: The population was stratified into sub case groups: prehistory only cases (pre cases), after TCA exposure only cases (after cases), and cases having prehistory AMI event and after exposure event (pre-post cases). RR was estimated using conditional Poisson regression to compare the rates of events during exposed periods with unexposed periods.

Results: In the stratified analyses, there were 556 (50.5%) pre cases and 460(41.8%) post cases in Clinformatics Data Mart, and there were 1931(62.4%) pre cases and 916(29.6%) post cases in OSIM2. Both databases showed the after cases had the lightest comorbidities; the pre-post cases had the worst comorbidities. In the pre-post cases, RR of AMI were stable as 1.8 (95%CI, 1.3–2.6) in Clinformatics Data Mart and 2.3 (95%CI, 1.9–2.7) in OSIM2. Somehow, prehistory positive cases showed overall protective effect of AMI: 0.3 (95%CI, 0.2–0.5) in Clinformatics Data Mart and 0.2 (95%CI, 0.1–0.2) in OSIM2. But when the three sub groups mixed in the final case pool, the results were going to different direction because proportions of pre cases were different in the two databases.

Conclusions: Overall, the results for the association between AMI and TCA exposure tested by SCCS were not consistent in these two databases. It is because TCA-AMI is a complex pair. The tested cases included different sub case groups. The most critical is the proportion of pre cases group, which showed AMI risk reduction from TCA exposure. This study provides some interesting evidence for the cautious method application in the nature of drug and outcome pairings and between different databases.

1021. Diffusion of Methodological Innovation in Pharmacoepidemiology: Self-Controlled Study Designs

Giulia P Consiglio,[1] Malcolm Maclure,[2] Lisa McCarthy,[1] Suzanne M Cadarette.[1] [1]*Leslie Dan Faculty of*

Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada.

Background: The field of pharmacoepidemiology has experienced significant methodological innovation, particularly in the last decade.

Objectives: To characterize the adoption of self-controlled (SC) study designs (case-crossover [CCO], case-time control [CTC], case-case-time control [CCTC], self-controlled case-series [SCCS]) in pharmacoepidemiology.

Methods: A systematic keyword (MEDLINE and EMBASE) and citation (Web of Science) search was completed to identify all empirical applications of SC designs in pharmacoepidemiology through to the end of 2013. Sociograms were generated to visualize the co-authorship network, examine components (distinct authorship groups), and identify cut-points (authors whose removal would increase the number of components). First and last author affiliations were identified to ascribe institutional contributions to each component, and the overall network.

Results: We identified 176 papers (79 CCO, 5 CTC, 1 CCTC, 85 SCCS, 6 combinations), by 763 unique authors since 1992. Few applications ($n=5$) were published before 2001, and half ($n=86$) were published from 2011 to 2013. The network comprised 46 components, yet 31 contained only one paper. The largest component contained 97 papers and was highly interconnected, attributable to similarities in study design (SCCS, 69%), country of institution (Canada, USA and UK comprised 57%), and collaborative seminal authors; Farrington (SCCS, 15 papers) and Suissa (CTC, 4 papers) were cut-points in the network. The second largest component contained nine papers, all from Taiwan-based institutions and published after 2010. The third largest component contained seven papers and seminal authors Maclure (CCO) and Wang (CCTC), with 42% attributed to Harvard University in Boston.

Conclusions: Adoption of SC innovations is increasing over time, yet no formal recommendations guide their use. Understanding the diffusion of SC designs in pharmacoepidemiology may identify critical factors supporting their adoption and thus potential targets, such as key opinion leaders, to develop and disseminate formal SC reporting guidelines.

1022. Does One-Size Fit All in Accounting for Immortal Time?

Evelyn M Flahvan,[1] Hu Li,[1] Claudia A Salinas,[1] Stephen P Motsko.[1] *[1]Global Patient Safety, Eli Lilly and Company, Indianapolis, IN, USA.*

Background: Immortal time (IT) is a period within a study in which, by design, death cannot occur. Bias introduced by the misclassification of IT has been discussed in the literature. Methods used to conduct analyses with IT include conditional analysis, time-fixed exposure, time-varying exposure, time-distribution matching, and inverse probability treatment weighting (IPTW). Some of these proposed best standards have been found to produce differing results due to their potential to introduce selection bias.

Objectives: To review analytical methods for IT and examine their impact in different scenarios.

Results: Cohort definition, exposure definition, and outcome can affect IT. Typically, cohort entry is disease-based. However, with chronic conditions (i.e., diabetes and depression), the accuracy of the diagnosis timing may vary considerably, modifying the amount of IT in an analysis and affecting results. In disease-based cohorts, time-fixed exposure introduces IT bias and time-varying exposure has been shown to mitigate the bias. However, the distribution of exposure dates and situations where the exposure is an intermediate between the baseline and outcome may introduce selection bias when using time-varying exposure definitions. Time-varying exposure is also subject to time-varying confounders, which IPTW may mitigate. Cox survival analyses are the most frequently used. The assumptions made in such models and the distribution of the outcome during follow-up should be closely examined. Study design can potentially remove issues, such as the varied amounts of IT due to timing of diagnosis, selection bias, or time-varying confounders. Exposure-based cohorts, with appropriately matched unexposed comparators, should be considered where possible. Examples of these different methods shall illustrate the impact of study and analytical design on bias from IT.

Conclusions: Inaccurate selection of a cohort, exposure definition, or analytic methods may potentially overcorrect biases introduced by IT. Thus, these methods need further research with respect to their application in different settings because one size most likely will not fit all.

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1023. Impact of Eligibility Length on Prevalence Estimates Using Automated Healthcare Claims Data

Yanmin Zhu, Wei Liu, Yan Li, Almut G Winterstein. *Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, USA.*

Background: Disease prevalence studies in claims data oftentimes alternate the requirement for the number of type of healthcare encounters but rarely consider the effect of eligibility windows.

Objectives: To examine the effect of varying length of eligibility periods on annual prevalence estimates of ADHD and to ascertain the effect of incomplete capture of encounter data in Medicaid managed care plans.

Methods: We used Medicaid extract files billing records to establish two samples of adults from 29 US states in 1999–2010. In the full sample, we restricted eligible subjects to the fee-for-service (FFS) patients from 1999 to 2006 but also included comprehensive managed care recipients from 2007 to 2010. In the FFS sample, we included only patients in FFS from 1999 to 2010. ADHD was identified based on ≥1 inpatient or two outpatient visits with ICD9-CM codes 314.xx. Eligible patients were required to have ≥12 months, 6 months, or 1 month continuous eligibility in the calendar year. We estimated prevalence of ADHD diagnosis in both samples.

Results: In the FFS sample, prevalence of adult ADHD continuously increased from 2.20 in 1999 to 10.57 per 1000 subjects in 2010 with 12 months continuous eligibility requirement. It increased from 1.77 to 8.68 and 1.17 to 4.42 per 1000 with 6 and 1 month continuous eligibility requirements, respectively. In the full sample, prevalence of diagnosed ADHD also increased from 1999 to 2010. The steady increase in ADHD prevalence was interrupted by a drop from 6.95 in 2006 to 5.18 in 2007 when we required 12 months continuous eligibility. This drop was less pronounced (3.43 to 3.34) in the sample with 1 month continuous eligibility requirement.

Conclusions: Period prevalence in claims data is strongly affected by eligibility requirements. With shorter continuous eligibility length requirement, the prevalence estimates tend to be underestimated due to the shorter risk period for ADHD diagnosis in each calendar year. Despite federal efforts to improve encounter capture of Medicaid beneficiaries in managed care plans, the steep secular incline of ADHD prevalence reversed when including comprehensive managed care recipients suggesting continued quality issues.

1024. Systematic Review of Adaptive Design Clinical Trials

Laura Bothwell, Nazleen Khan, Aaron Kesselheim. *Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA.*

Background: Adaptive design clinical trials involve assessing preliminary results of a trial at a pre-set interim point and adapting study design in response. There have been no rigorous assessments of the scope of adaptive design used in clinical trials.

Objectives: Describe trends in use of adaptive design trials.

Methods: Systematic review of adaptive design trials in PubMed, EMBASE, Cochrane, and Web of Science databases through October 2014. We extracted information on date, location, duration, impact factor, funding, author affiliations, intervention type, sample size, and whether trials found statistically significant results. Findings were compared with available data on non-adaptive trials.

Results: Review yielded 2439 results; 109 were relevant. Eighty-five percent was published after 1998. Forty-three percent were carried out in Europe, 24% in USA, 24% multinational, and 9% elsewhere. Mean trial duration was 95 weeks. Trials were cited 58 times, on average. Fifty-two percent was funded by industry, 16% by governments, 13% other funding schemes, 19% did not list funding. Fifty-three percent of authors were primarily affiliated with academia/health care institutions, 27% industry, 19% private foundations, 1% government. Eighty-one percent of trials tested pharmaceutical products, 12% other interventions, 7% medical devices. Average subject sample size was 346. 65% and had statistically significant results.

Conclusions: Adaptive design trials have been increasingly used since the late 1990s. Europe has produced the most adaptive trials, followed by the US, though adaptive trials represent a larger portion of overall trials in Europe than in the USA. A significant portion of authors were affiliated with or funded by

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industry, indicating industry has had a significant role in encouraging adaptive designs. The trials have been reasonably cited in subsequent literature, indicating they have drawn scientific interest. They have had reasonable sample sizes relative to standard phase II trials, but smaller relative to standard phase III trials, indicating that phase III adaptive trials may be less costly but also less rigorous than standard phase III trials. Finally, average duration of adaptive trials reflected average length of standard trials, despite claims that adaptive trials are faster.

1025. Comparison of Case-Only Designs with Traditional Study Designs: A Systematic Review

Koen B Pouwels,[1] Bianca Mulder,[1] Eelko Hak.[1] [1]*Unit of PharmacoEpidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, The Netherlands.*

Background: It is increasingly common to compare estimates from case-only designs with those obtained with more traditional designs such as the cohort and case–control studies to gain an indication about the potential influence of unmeasured confounders.

Objectives: We aimed to evaluate the concordance between case-only and case–control or cohort studies in empirical studies and to identify predictors of discrepancies between both types of designs.

Methods: The MEDLINE and EMBASE databases were searched through 31 June 2013. Epidemiological studies that used both a case-only and a case–control or cohort design were identified. Of all included studies, general study characteristics, effect estimates and potential predictors of discrepancies between both types of designs were extracted. Spearman correlation coefficient was used to evaluate the concordance between case-only and cohort or case–control studies. Z-scores were used to assess whether difference in the effect estimates were beyond what would be expected by chance alone. Subsequently, a prediction model was built using multivariable logistic regression to assess whether such discrepancies could be predicted.

Results: The search identified 1367 unique articles, of which 57 articles were included for analysis. In total, 526 comparisons were made between case-only and cohort or case–control designs. The correlation coefficient between the treatment effect in case-only and cohort or case–control studies was 0.63 ($p < 1e{-}15$). In 226 of the 526 comparisons (43%), the difference between both study designs was beyond what would be expected by chance alone. Backward selection based on the AIC resulted in a final model including the following predictors: intermittent exposure, rare event, acute outcome, length of hazard period, type of case-only design and sample size of the traditional study design. This model had a c-statistic of 0.790 (95%CI 0.752–0.827)

Conclusions: The correlation between effect estimates of case-only and cohort or case–control design is moderate, and discrepancies beyond chance are very common. Such discrepancies could be predicted by failure to meet important assumptions of case-only designs.

1026. Extent of Publication Bias in Observational Studies Investigating Adverse Drug Events

Dixa B Thakrar,[1] Iain D Tatt,[2] Mikkel Z Oestergaard.[2] [1]*School of Medicine, University of Leicester, Leicester, UK;* [2]*Biometrics, Roche, Basel, Switzerland.*

Background: Clinical trials have limited ability to detect safety concerns. Hence, ongoing monitoring of safety is critical in pharmacovigilance. Observational studies help inform assessment of safety but are subject to reporting biases, like publication bias, which may distort interpretation of data.

Objectives: To evaluate the extent of publication bias in adverse event (AE) reporting in observational studies.

Methods: A systematic review of observational studies was conducted, using the example of Rituximab (RTX) in approved oncology and autoimmune (AI) indications. Reporting of prespecified risks (neutropenia, thrombocytopenia (TCP) and infusion-related reactions (IRR) in oncology; and neutropenia, IRR and HBV reactivation in AI) was evaluated for publication bias, with funnel plots and Egger's test (y-intercept = 0 for regression of normalized effect size vs. precision). Combinations of indication, AE, AE grade and treatment where there were ≥10 studies were included. Impact of variables like disease subtype, sex, study quality and geography on asymmetry was also evaluated.

Results: Nine combinations had ≥10 studies and were included. Egger's test revealed asymmetry in studies reporting incidence rates of grade 3–4 TCP ($n = 19$;

intercept = −3.59; $p = 0.01$) in NHL patients taking any treatment. For studies observing patients on RTX, publication bias was evident in TCP (all grades: $n = 12$; −4.79; 0.03 and grade 3–4: $n = 12$; −4.45; 0.02) in NHL patients. Of borderline significance were studies on IRR in AI ($p = 0.1$). Much of the asymmetry was explained by disease subtype, sex, geography subgroups for NHL; and follow-up time, geography, study quality subgroups in AI.

Conclusions: While initial tests for publication bias showed some evidence in NHL and AI, analyses by subgroups largely explained asymmetry. Bias, both publication related and due to heterogeneous populations should be explored in systematic reviews of safety data. We have demonstrated the value of assessing publication bias through funnel plots, Egger's test and considering other sources of bias in systematic reviews for pharmacovigilance across more than one approved indication.

1027. Application of Indirect Treatment Comparison Method for Pooling Data from Clinical Trials for Benefit-Risk Assessment

Sampada K Gandhi, Lili Wang, Juhaeri Juhaeri. *Global Pharmacology & Epidemiology, Sanofi U.S., Bridgewater, NJ, USA.*

Background: Due to the increasing need for benefit risk (BR) assessment, data pooling is needed to compare BR profile of various drugs. Data from four clinical trials of drug A with three comparators (drugs B, C and D) conducted in type 2 diabetic patients were used for a BR assessment. Due to the differences in study duration, comparators and baseline patient risks, comparing the results of BR criteria of drug B in the AB trial directly to those of drug C in the AC trial may introduce bias. In order to minimize this bias, indirect treatment comparison (ITC) method was applied to pool the trial data for the BR assessment.

Objectives: To describe the methodological approach, ITC, used for pooling the clinical trial data and to compare the results with direct pooling.

Methods: Data for selected categorical and continuous BR criteria were obtained from four clinical trials. Incidence rate ratios (IRRs) for categorical BR criteria and differences in mean changes for continuous BR criteria, comparing drugs B, C and D with referent drug A, respectively, were estimated. Combined incidences rates (IRs) and mean changes for BR criteria among drug A users from four trials were computed. Final IRs and mean changes for drugs B, C and D were calculated by multiplying the combined IR for each categorical criterion for drug A with IRR's or adding the combined mean change for each continuous criterion for drug A to differences in mean changes for the same criterion for drugs B, C and D. Data pooled directly from trials were compared with the data pooled using ITC.

Results: The IRs and mean changes for drugs B, C and D obtained after application of ITC showed a change up to 15% from the direct pooling estimates and estimates were comparable for most criteria. However, 95% confidence intervals (CIs) for ITC estimates were wider compared to the CI's obtained from direct pooling.

Conclusions: The results from direct pooling and ITC methods are different. Application of ITC may provide an unbiased alternative to pool clinical trial data.

1028. Use of Natural Language Processing (NLP) to Identify Patients with Binge Eating Disorder (BED) in Optum's Humedica Research Database

Kathleen M Mortimer, Baevin S Carbery, Robert V Gately, Dave D Dore. *Epidemiology, Optum, Waltham, MA, USA.*

Background: There is increasing interest in NLP within electronic health records (EHRs) to identify patients with conditions, such as binge eating disorder (BED), which have no specific ICD-9 diagnosis codes.

Objectives: To explore the capability to identify and characterize patients with BED via the free text notes of Optum's Humedica Research Database.

Methods: Free text in the notes within patient EHRs was extracted into unique fields: *section* (e.g. history of illness), *fact type* (e.g. observation by physician), *concept head/token of interest* (e.g. binge eating), *qualifiers* (e.g. recurrent) and *fact sentiment* (e.g. deny). Patient notes with terms suggestive of binge eating disorder were identified. The relative frequency of the terms and associated qualifiers and sentiments was summarized.

Results: The frequency of select concept head terms was binge (30%), binge eating (21%), food issues (18%), bulimia (20%), bulimia nervosa (8%), binge

eating disorder (1%), compulsive eating (1%) and eating binge (0.4%). One-third of the observations had additional fact classifications; the most common were negations (19%) and recommendation to avoid (6%). Qualifiers (attributes) were reported for only 12% and included frequency (e.g. some, occasional) and attributions of the concept head to family members.

Conclusions: BED and binge eating behavior terms are observed in patient EHRs, but care must be taken to identify negations and attributions that refer to a patient's family member or history. Additionally, a wide variety of terms must be used to identify potential cases and may have varying levels of specificity.

1029. Withdrawn by author

1030. Utility of Linked Data in Controlling for Confounding by Indication: A Case of Cardiovascular CER Using Propensity Score Adjustment

Soko Setoguchi,[1] Hiraku Kumamaru,[2] Lauren Williams,[3] Jalbert J. Jessica.[4] *[1]Duke Clinical Research Institute, Durham, NC, USA; [2]Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [3]Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA, USA; [4]LA-SER Analytica, New York, NY, USA.*

Background: Linking claims and registry data may overcome shortcomings in either data source. However, the utility of linked data combined with advanced analytic methods, such as high dimensional propensity score (hdPS), to overcome confounding by indication is not clear.

Objectives: To assess how comparative effectiveness estimates change when combining additional clinical and provider information with different PS techniques when comparing carotid stenting (CAS) to carotid endarterectomy (CEA).

Methods: The study population consisted of Medicare fee-for-service beneficiaries ≥66 years of age who had undergone CAS/CEA between 2005 and 2008, who were linked to Society for Vascular Surgery's Vascular Registry (SVS-VR). We derived various PS: (1) investigator-specified (IS-PS) with claims variables and/or registry variables, (2) hd-PS using claims information and/or registry variables including symptoms, imaging results, pre-procedural medications, and high-surgical risk status. We estimated hazard ratios (HR) for CAS versus CEA using Cox regression adjusting for the PS by trimming. We assumed that the "true" HR was 1, based on landmark clinical trials CREST and SAPPHIRE.

Results: The study included 1999 CAS and 3255 CEA patients (mean age: 76.1 years; 59.3% male; 93.3% white). More CAS patients were at high-surgical risk than CEA patients. PS model discrimination was lowest for the IS-PS (0.67; claims only) and highest for PS including registry information (0.96). Adjusting for PS corrected the upward bias and drove the CEEs downwards. Relative to crude estimates (HR = 1.82), claims only or registry only IS-PS were ~1.4, which was similar to claims-only or registry-only hd-PS CEEs. When both claims and registry data were used, IS-PS HR was 1.21 and hd-PS HR was 1.18, much closer the results expected based on RCT evidence. With further adjustment with provider level variables, the HR was 1.02.

Conclusions: Both claims and registry data were necessary to control for confounding by indication in the comparison of CAS versus CEA, even with the used of advanced analytic techniques.

1031. Completeness of Key Variables in the Clinical Practice Research Datalink (CPRD)

Emily Herrett,[1] Arlene Gallagher,[2,3] Krishnan Bhaskaran,[1] Harriet Forbes,[1] Rohini Mathur,[1] Tjeerd van Staa,[1,3,4] Liam Smeeth.[1] *[1]London School of Hygiene and Tropical Medicine, London, UK; [2]Clinical Practice Research Datalink, London, UK; [3]Utrecht University, Utrecht, The Netherlands; [4]University of Manchester, Manchester, UK.*

Background: The Clinical Practice Research Datalink (CPRD) is an ongoing primary care database of anonymised medical records from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK. CPRD is broadly representative of the UK general population in terms of age, sex and ethnicity, but the completeness of data items frequently used in epidemiological research studies has not been described.

Objectives: To measure completeness of smoking, blood pressure, body mass index (BMI), alcohol intake, total cholesterol and ethnicity over time.

Methods: Based on a random sample of one million adult CPRD patients, completeness of smoking, blood pressure, BMI, alcohol intake, total cholesterol and ethnicity was assessed annually between 1988 and 2013, and stratified by age and sex. Denominators were calculated based on the number of patients that were registered at each midyear (2 July). Analyses estimated the proportion of patients with a record in the past three calendar years, and the proportion where a record had ever been made.

Results: Completeness of all variables increased over time. By 2013, data were available in 95% of patient records for smoking status, 86% for blood pressure, 80% for BMI, 77% for alcohol intake, 51% for total cholesterol and 48% for ethnicity, respectively. When restricted to recording in the last three years (excluding ethnicity, which does not change over time), these proportions decreased to 79% for smoking status, 72% for blood pressure, 52% for BMI, 63% for alcohol intake and 39% for cholesterol, respectively. Completeness of these measures was lower in men and women aged below 65 years. However, despite lower completeness, at least 50% of patients in the 18–65 years age group had records of smoking, blood pressure and alcohol within the previous 3 years.

Conclusions: Quantifying the completeness of these key epidemiological variables is of value to researchers using the CPRD and to those interpreting CPRD studies using these data items.

1032. Utilizing Electronic Medical Record Networks and Advanced Analytics for Identifying Patients for Clinical Trial Recruitment

Spencer Justin, Andrew Wilson, Nicole Bailey, Matthew Longson, Aaron Kamauu. *Anolinx, LLC, Salt Lake City, UT, USA.*

Background: Much of the increase in healthcare expenses in the USA can be traced to the development of new drug therapies, with the average discovery and development process costing over $1.4 billion per drug. This motivates the need to reduce drug costs through more efficient drug development and testing, specifically, by streamlining clinical trials.

Objectives: To develop, implement and evaluate a process, using a data driven approach, to recruit patients for a clinical trial for an asthma treatment. Our hypothesis is that patient recruitment is improved and accelerated with the support of an EMR network.

Methods: Trial protocol eligibility criteria were reviewed. Key criteria were translated into query definitions and queried against our EMR network. Query results were stratified by healthcare institution and organized into a funnel model representing the relative impact of each criterion. Final patient count results were further stratified by distinct hospital unit or clinic (location) and represented by geographic distribution. Adjustable patient recruitment parameters were also applied to location-specific results, to identify potential clinical trial sites mostly likely to recruit the highest patient concentrations.

Results: EMR queries identified over 300 potentially eligible patients at three different sites. Of identified patients who were contacted, and for whom information was available, 84% responded to outreach efforts, which represents a very substantial increase over the 10% that is typical in the industry. Among respondents, enrollment rates ranged from 14% to 40%.

Conclusions: For all participating sites, querying EMR data proved to be an effective means of identifying eligible patients. Furthermore, once candidates were identified, all recruitment efforts could be directly targeted to specific patients as opposed to advertising to a large, undefined population or relying on physician referral. This resulted in improved patient response rates, which could conceivably be improved further with the creation of more targeted recruitment materials developed by patient demographic profiles generated from EMR data.

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