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ICPE 2012 Abstracts

1. Using Mailed-In Capillary Blood Samples to Detect Diabetes in Community-Dwelling Adults: Evaluation of an Innovative Strategy

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Background: A large proportion of diabetic people are unaware of their condition and many are in the prediabetic state and are at high risk of diabetes and diabetes-related complications.

Objectives: We evaluated an approach that offers the potential for widespread population-level screening for pre-diabetes and diabetes through fasting glucose sampling at home.

Methods: We surveyed a random sample of the general population of Quebec, 20 years of age and older. We collected data on diabetes, socio-demographic information, lifestyle habits, and use of health care services. Participants responded to a telephone and/or postal survey and provided a fasting capillary blood glucose sample using lancets received in the mail. A drop of blood was applied to the filter paper provided and returned by mail to the central lab, where glucose assessments were performed.

Results: A random sample of 6,247 individuals was generated by the Health Insurance Agency of Quebec. Among these, 3,506 (57.4%) responded to the questionnaire and 1,629 (44.9% of respondents) provided analyzable blood samples. Among the individuals who were not previously diagnosed with diabetes or plasma glucose intolerance, 1,088 (79.3%) had fasting plasma glucose (FPG) ≤6 mmol/L (normal), 220 (15.6%) had FPG 6.1–7.0 mmol/L (prediabetics) and 68 (5.2%) had FPG >7.0 (undiagnosed diabetes); 21.1% of the undiagnosed diabetes group and 23.4% of the prediabetic group were younger than 40 years of age and about 24% of them did not visit their physician yearly and may have been therefore unlikely to be diagnosed in a health care setting unless they developed symptoms. Among the 182 patients with self-reported diabetes who provided blood samples, 67 (36.8%) had FPG >7. Most of these patients (89.6%) reported using antidiabetes drugs or insulin.

Conclusions: A substantial proportion of Canadians with type2 diabetes or pre-diabetes remain undiagnosed. Introduction of an FPG sampling at home could identify prediabetic and undiagnosed diabetic individuals who otherwise would not be detected. Among diabetic patients who provided blood samples, many had inadequate glycemic control.

2. Prevalence of Known Complications of Diabetes: A Comparison between Large EHR and Claims Databases in the U.S.

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Background: Type 2 Diabetes Mellitus (T2DM) is a leading cause of renal failure, lower limb amputation, new cases of blindness, heart disease and stroke, and is the 7th leading cause of death in the United States. While qualitative knowledge of T2DM sequella is well understood; quantitative analysis of these complications in large commercially-available observation databases, is limited from current literature.

Objectives: To compare prevalence of known T2DM complications between the GE Centricity (GE) EHR and Thomson Reuters MarketScan claims databases.

Methods: Patients who were at least 18 years old at the first diagnosis of T2DM (ICD-9 codes: 250.x0 and 250.x2) were included in the study. A comprehensive list of more than 173 known T2DM complications were organized into 12 categories according to high-level organ systems and identified by ICD-9 codes in both databases.

Results: In the GE database, 1,241,562 patients (52% females, mean age 60.0 years SD 13.7) met the inclusion criteria compared with 7,092,249 patients (49% females, mean age 56 years SD 13.8) in MarketScan. Of the five most prevalent complications in each database, three were common to both, namely (GE vs. MarketScan), Infections (20.6% vs. 34.9%), vascular diseases (21.2% vs. 25.9%), and orthopedic disorders (17.8% vs. 25.8%). In contrast, renal disorders (15.4% vs. 12.2%) and neuropathy (13.2% vs. 15.4%) made up the top five prevalent conditions in GE compared with ophthalmic disorders (10.2% vs. 25.8%) and metabolic disorders (6.6% vs. 21.7%) in MarketScan.

Conclusions: Some rates of T2DM complications were similar, while others were different between the databases. This finding has potential important implications for interpreting PE studies. Therefore, further studies are needed to better understand if these differences are due to differences in patient characteristics or to some inherent difference in the way the data are captured.

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3. Population Attributable Risk of Macrovascular Events Associated with HbA_{1c}, Blood Pressure or Weight in Patients with Type 2 Diabetes Mellitus

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Background: Diabetes guidelines define targets for HbA_{1c}, systolic blood pressure (SBP), or weight (body mass index, BMI), but to what extent they each contribute to diabetes complications is largely unknown.

Objectives: To determine the population attributable risk (PAR) of macrovascular events associated with HbA_{1c}, SBP, or BMI in patients with type 2 diabetes mellitus (T2DM).

Methods: The population-based PHARMO database contains T2DM patients regularly monitored in primary care for cardiovascular risk factors HbA_{1c}, SBP and BMI. In the period 2000–2008 patients without baseline macrovascular events and on antidiabetic treatment for ≥6 months were followed 1 year from start of monitoring to end of monitoring data (median 25 months, IQR 9–51). Multivariate survival modeling of the composite outcome of macrovascular events was used to estimate the expected number of events after 5 years, either with unchanged risk factors (base-case) or with modeled reductions in risk factors. The PAR was calculated as the number of averted events divided by the number of expected events in the base-case analysis.

Results: Mean age of 5,841 included patients was 66 years, 55% was male, 45% had HbA_{1c} levels ≥7%, 66% had a SBP ≥140 mmHg and 85% had a BMI ≥25 kg/m^2. The base-case expected number of macrovascular events at 5 years was 796, and 687 after reduction to target of all three risk factors. The combined PAR of elevated HbA_{1c}, SBP and BMI was 14%, ranging from 5% among those with one elevated risk factor to 21% among those with three risk factors elevated. Incremental reductions of 0.5% HbA_{1c}, 10 mmHg and 10% BMI lead to 4% fewer events, ranging from 2% to 10%. The PAR of reducing HbA_{1c} to target (7%) was 5%, ranging from 2% to 10%. The PAR of reducing SBP to target (135 mmHg) was 9%, ranging from 3% to 12%. There was no effect of reduction in BMI alone.

Conclusions: Reducing elevated HbA_{1c} and blood pressure levels was associated with improvements in cardiovascular risk. Even modest reductions in risk factors lead to significant reductions in macrovascular events in T2DM patients.

4. Population Attributable Risk of Microvascular Events Associated with HbA_{1c}, Blood Pressure or Weight in Patients with Type 2 Diabetes Mellitus

Edith M Heintjes,[1] Fernie JA Penning-van Beest,[1] Shreekant V Parasuraman,[2] Susan Grandy,[2] Mike Pollack,[2] Ron MC Herings.[1,3] *[1]PHARMO Institute, Utrecht, Netherlands; [2]HEOR, AstraZeneca Ltd., Wilmington, DE, United States; [3]Medical Informatics, Erasmus University Medical Centre, Rotterdam, Netherlands.*

Background: The contributions of HbA_{1c}, systolic blood pressure (SBP), or body mass index (BMI) to diabetes complications are largely unknown.

Objectives: To determine the population attributable risk (PAR) of microvascular events associated with HbA_{1c}, SBP, or BMI in patients with type 2 diabetes mellitus (T2DM).

Methods: The population-based PHARMO database contains T2DM patients regularly monitored in primary care for cardiovascular risk factors HbA_{1c}, SBP and BMI. From 2000 to 2008, 6,010 patients on antidiabetic treatment for ≥6 months were followed 1 year from start to end of monitoring data (median 25, interquartile range [IQR] 9–51 months). The expected number of complications (moderate-severe renal failure, retinopathy, ulcers with or without amputations) after 5 years were estimated using multivariate survival models based on registered complications, risk factors and other characteristics (base-case). The estimated number of averted cases after reducing risk factors divided by the base-case number resulted in the PAR.

Results: Mean age was 66 years (SD ±12), 55% were men. Forty-five percent had elevated HbA_{1c} (≥7.0%), with an average of 7.8% (±0.8). HbA_{1c} reductions of 0.5% or to target <7.0%) led to significant case reductions of renal failure of 3% and 5% and of retinopathy by 6% and 10%, respectively. Sixty-six percent had elevated SBP (≥140 mmHg), with an average of 161 mmHg (±16). SBP was not significantly associated with microvascular complications. Eighty-five percent had elevated BMI (>25.0 kg/m^2) with an average of 30.7 kg/m^2 (±4.5). BMI reductions of 10% (mean 8.7 kg) or to target (25.0 kg/m^2, mean 15.8 kg) led to significant case reductions of ulcers of 20% and 35%, but an increase of retinopathy of 7% and 12%, respectively. Eliminating all risk factors in the model would have averted 99 out of 493 renal failure cases (PAR 20%), 148 out of 566 ulcer cases (PAR 26%) and 21 out of 580 retinopathy cases (PAR 4%) after 5 years. Reductions of 0.5% HbA_{1c}, 10 mmHg SBP and 10% BMI would have averted 11% of renal failure,16% of ulcers and 1% of retinopathy.

Conclusions: Modest changes in HbA_{1c} and BMI led to significant reductions in microvascular complications.

5. Clinical and Economic Benefits of Lowering Severely High Triglycerides on Cardiovascular Events, Pancreatitis, and Diabetes among Patients with Type 2 Diabetes Mellitus

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Background: The impact of reducing severely high triglyceride (SHTG; ≥500 mg/dL) levels among patients with Type 2 diabetes mellitus (T2DM) is unknown.

Objectives: To quantify the clinical and economic effects of reducing SHTG levels among patients with T2DM.

Methods: Utilizing two large US healthcare claims databases, we identified 13,085 T2DM patients (pts) (≥18 years) with SHTG from 2001 to 2010, who maintained continuous enrollment with medical and pharmacy claims for ≥6 months before their index SHTG lab value. Of these, we identified 3,245 pts whose triglycerides (TGs) remained elevated (≥500 mg/dL) and 9,840 pts whose TGs dropped to below 500 mg/dL within 6–24 weeks after their first TG ≥500 mg/dL. We examined pt data after their second TG level and assessed the following outcomes: cardiovascular (CV) events, hospitalization/ER visits for diabetes, pancreatitis, all-cause and CV-related costs. Crude and adjusted multivariate Cox proportional hazards models were developed for each clinical outcome. Costs were computed as total paid amounts, inflation-adjusted to reflect 2010 costs, and analyzed using Lin's regression.

Results: T2DM pts whose TGs remained elevated above 500 mg/dL were 1.13 times more likely to have a CV event (95% CI: 1.02–1.25), 1.84 times more likely to experience acute pancreatitis (95% CI: 1.37–2.47), and 1.35 times more likely to have a hospitalization or ER visit for diabetes (95% CI: 1.19–1.52) compared to pts whose TGs dropped below 500 mg/dL, after adjusting for important confounders. Adjusted all-cause cumulative total costs were significantly lowered by $1,557 (year 1), $3,388 (years 1–2), and $4,843 (years 1–3) per T2DM pt whoseTG levels dropped to < 500 mg/dL. Substantial reductions in costs were also observed for adjusted cumulative CV-related costs ($1,008 – year 1, $1,638 years 1–2, $2,074 years 1–3).

Conclusions: These findings provide evidence that when TG levels drop below 500 mg/dL, rates of CV disease, pancreatitis, diabetes-related hospitalizations and ER visits are reduced and this may translate into substantial reductions in costs for pts with T2DM.

6. Risk Factors for Incident Diabetic Retinopathy in Type II Diabetes in UK Primary Care

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Background: Diabetic retinopathy (DR) is a leading cause of blindness in the working-age population in UK. Glycaemia control is determinant in the natural history of eye disorders but even under well-controlled diabetes there is increased risk of DR.

Objectives: To estimate the DR incidence rate (IR) and identify risk factors for incident DR in type II diabetes in the context of current management of diabetes in UK primary care.

Methods: We conducted a case-control analysis nested in a cohort of newly diagnosed type II diabetes patients aged 1–84 years identified in The Health Improvement Network (THIN) database between 2000 and 2007. We followed patients until DR code (N = 7,735), age 85 years, death, or 31/12/2008. DR diagnosis was confirmed by general practitioners in 72% of instances. Cases were all patients with DR and controls were a random sample of study cohort (N = 9,395). Adjusted odds ratios (OR; 95% CI) were estimated for life-style and medical factors, and hypoglycemic drugs.

Results: The DR IR was 23.8 per 1,000 person-years (95% CI: 23.17–24.43). The risk of DR increased with diabetes duration, although 21% of cases were identified at first diabetes diagnosis. DR increased slightly with systolic BP ≥140 mmHg (OR 1.14; 1.07–1.21), high alcohol consumption (OR 1.34; 1.11–1.61), glycated haemoglobin (HbA_{1c}) (OR 9–10% 1.14; 1.00–1.31; OR 10–11% 1.25; 1.07–1.45;OR ≥ 11% 1.21; 1.07–1.37) and retinal venous occlusion (OR 2.47; 1.67–3.66). History of glaucoma was associated with an OR of 0.71 (0.60–0.84). Patients with HDL ≥1.55 mmol/L (OR 0.88; 0.80–0.98), triglycerides ≥1.7 mmol/L (OR 0.89; 0.83–0.96) or current smokers (OR 0.89; 0.81–0.97) presented a slightly reduced risk. Proteinuria, BMI, cholesterol or LDL were not associated with diagnosis of DR. Use of metformin (OR 1.21; 1.13–1.30), sulphonylureas (OR 1.25; 1.15–1.36) and insulin (OR 1.50; 1.30–1.74) showed an increased risk of DR.

Conclusions: A proportion of DR was found at first diabetes diagnosis suggesting late diabetes diagnosis. Multiple factors appeared to be associated with DR, including high HbA_{1c}, systolic BP, alcohol consumption and use of hypoglycemic drugs. High HDL appeared to confer a reduced risk.

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7. Investigating the Prevalence and Causes of Prescribing Errors in General Practice: The PRACtICe Study

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Background: Prescribing errors are known to be an important cause of morbidity and mortality in primary care and yet there have been few large-scale studies investigating the prevalence of these errors.

Objectives: To determine the prevalence of prescribing and monitoring errors in general practices and to explore the factors associated with these errors.

Methods: Observation study involving retrospective review of a 2% random sample of patients' healthcare records over a 12 month period. Data were collected by four pharmacists who were specially trained to identify potential errors.

Setting: Fifteen English general practices.

Exposures: Characteristics of general practices, patients, or prescriptions.

Main outcome measures: Presence of prescribing errors or monitoring errors (defined as failure to undertake blood tests within recommended time limits + 50%)

Statistical analysis: Descriptive analyses were conducted in Stata, Version 11.2, as were modelling analyses of the factors associated with error using mixed effects logistic regression techniques.

Results: The records of 1,777 patients were examined. Collectively, the pharmacists reviewed 6,048 unique prescription items. There were 247 prescribing errors and 55 monitoring errors. The percentage prevalence of prescriptions with prescribing or monitoring errors was 4.9% (95% confidence intervals 4.4–5.4%). The most common types of prescribing error were "incomplete information on the prescription" (74; 30.0%); "dose/strength errors" (44; 17.8%) and incorrect timing of doses (26; 10.5%). The following factors were associated with increased risk of prescribing or monitoring errors: male gender, age < 15 years or > 64 years, number of unique medication items prescribed, and being prescribed preparations in several therapeutic areas including cardiovascular, infections, immunosuppression, and musculoskeletal.

Conclusions: Prescribing or monitoring errors are reasonably common in general practice. Having identified the most common types of error and the factors associated with these, it will be possible to design strategies aimed at tackling the most important prescribing safety problems.

8. General Practitioner (GP) Variability in the Prescribing of Potentially Inappropriate Medication in Older Populations in Ireland

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Background: Prescribing indicators have become a common feature in many health care systems in an attempt to reduce unwarranted physician variation in medical care, improve quality and control drug costs.

Objectives: This study aimed to: (1) estimate the variation in potentially inappropriate prescribing (PIP) across GPs in an Irish older population using the STOPP criteria; (2) estimate how reliably the criteria could distinguish GPs in terms of their proportion of PIP and (3) examine patient and GP characteristics associated with PIP in a multilevel regression model.

Methods: Of 2,046 GPs with 338,375 registered patients' ≥70 years were extracted from the Health Service Executive Primary Care Reimbursement Service (HSE-PCRS) pharmacy claims database. HSE-PCRS prescriptions are WHO ATC coded. Details of every drug dispensed and demographic data for claimants' and prescribers' are available. Thirty PIP indicators (STOPP) were applied to prescription claims in 2007. STOPP is a screening tool of older persons' PIP assessing drug–drug and drug–disease interactions, dose and duration. Multilevel logistic regression examined how PIP varied between GPs and by individual patient and GP level variables.

Results: The overall prevalence of PIP was 36% (GP level data, median 35%, interquartile range 30–40%). The STOPP criteria were reasonably reliable measures of PIP (average > 0.8 reliability for 90% of GPs). The multilevel regression model found that only the patient level variable, number of different repeat drug classes was strongly associated with PIP (> 2 prescribed drugs for ≥3 months *v* no drugs; odds ratio 4.0, 95% confidence interval 3.7–4.3). Other patient level variables were significantly associated with PIP but became non-significant in the adjusted multilevel model. After adjustment for patient level variables the proportion of PIP varied by fourfold (half to twice the expected proportion) between GPs. This was not explained by GP level variables.

Conclusions: Polypharmacy is an independent predictor for PIP and interventions aimed at enhancing appropriateness of prescribing amongst GPs should target patients taking multiple medications.

9. Guiding Therapy for Uncomplicated Urinary Tract Infection (UTI)

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Background: US treatment guidelines for uncomplicated UTI in women recommend avoiding trimethoprim/sulfamethoxazole (TMP/SMX) in populations where resistance exceeds 20%. This has led to expanded use of second-line agents, such as fluoroquinolones, for which resistance is increasing.

Objectives: Characterize TMP/SMX use for UTI and develop a prediction model to identify patients at high risk of TMP/SMX treatment failure.

Methods: A retrospective cohort study of adult, female primary care outpatients with suspected UTI was conducted in a health maintenance organization in 2010. Patients were classified as high risk of treatment failure with empiric TMP/SMX if they had a positive urine culture for a pathogen meeting any of the following conditions: (1) TMP/SMX non-susceptible, (2) innately not covered by TMP/SMX, or (3) insufficient microbiology testing to verify TMP/SMX susceptibility. Logistic regression was used to develop a prediction model for this outcome with patient characteristics, comorbidities, and history of antimicrobial use, infection, and healthcare encounters as potential predictors. Model selection was based on maximizing and minimizing the c-statistic and AIC, respectively. We also described pathogens cultured, antimicrobial resistance patterns, and prescribed antimicrobials.

Results: Of 14,451 patients in the cohort, 2,098 (15%) had high risk of TMP/SMX treatment failure. Overall, 25% were treated with TMP/SMX; among those at low risk treatment failure, only 26% received TMP/SMX. The final prediction model (c = 0.59) included age ≥65 years (OR = 1.46, 95% CI: 1.33, 1.61), any antibiotic use in past 60 days (OR = 1.62, 95% CI: 1.44, 1.83), UTI with TMP/SMX non-susceptible *Escherichia coli* in past year (OR = 3.75, 95% CI: 2.96, 4.75) and UTI in past year (OR = 1.11, 95% CI: 1.01, 1.24). The maximum specificity achieved with this model was 98%, while maximum sensitivity was 55%.

Conclusions: A prediction rule to guide empiric TMP/SMX therapy of UTI could reduce unnecessary broad-spectrum antibiotic use and limit the spread of resistance. Additional predictors and alternate modeling techniques are being evaluated to increase model accuracy.

10. Trends in Antidepressants and Tamoxifen Co-Prescribing among Women with Breast Cancer, 2004–2010

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Background: Among tamoxifen users breast cancer recurrence risk may be increased with concomitant strong CYP2D6 inhibitor use, including some antidepressants. In October 2006 an FDA advisory committee recommended this interaction be listed on tamoxifen's label, and clinical guidelines recommend avoiding taking strong inhibitors with tamoxifen.

Objectives: Describe trends in co-prescribing antidepressants with tamoxifen and evaluate patient and treatment characteristics associated with strong inhibitor use following the 2006 FDA advisory committee meeting.

Methods: Using MarketScan claims we created a retrospective, longitudinal cohort of 11,925 women aged 50–95 with breast cancer initiating tamoxifen between 2004 and 2009. We propensity score matched patients initiating tamoxifen with patients initiating aromatase inhibitors to estimate changes in co-prescribing, accounting for secular trends. We used generalized estimating equations to model relative changes in co-prescribing over the study period.

Results: In each month, 24% of tamoxifen and aromatase inhibitor users were prescribed antidepressants. Among women using tamoxifen and antidepressants, 33% used strong inhibitors before October 2006 compared with 15% in 2010. Strong inhibitor use decreased among all endocrine therapy users, but more rapidly among tamoxifen users. Relative to aromatase inhibitor users, tamoxifen users were 43% less likely to use strong inhibitors by 2010 (Ratio of Risk Ratios [RRR] 0.57, 95% Confidence Interval [CI] 0.43–0.74). Weak inhibitor use increased among tamoxifen users from 33% of women between 2004 and 2006 to 50% in 2010, increasing more rapidly than among women on aromatase inhibitors (RRR: 1.47, CI: 1.23–1.76). The factor most strongly associated with strong inhibitor and tamoxifen co-prescribing after 2006 was prior strong inhibitor use (RR: 4.35, CI: 3.34–5.66).

Conclusions: Despite substantial declines in strong CYP2D6 inhibitor use among tamoxifen users, these agents continued to be used by nearly 15% of antidepressant users. Additional efforts should be made to ensure that women receiving combination therapy are aware of the potential risks and discuss alternative therapies with their providers.

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11. Acetaminophen Use Patterns Associated with Excess Dosing

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Background: Excess use of acetaminophen is linked to liver injury. Use of 500 mg acetaminophen medicines and OTC medicines combining acetaminophen and other ingredients are thought to contribute to over-dosing, but little is known about patterns of use leading to excess dosing.

Objectives: To determine patterns of use associated with exceeding the recommended daily maximum dose of 4 g acetaminophen.

Methods: Of 3,618 US adults from an on-line research panel completed on-line medication diaries for seven consecutive days in summer 2010. People with low education were under-represented. We computed total daily acetaminophen intake on 13,852 days of use and noted deviations from label instructions. GEE analyses compared patterns on days use was >4 g vs. days ≤4 g.

Results: >4 g days almost always (92%) involved other label deviations, such as re-dosing medication too soon (72%), concomitant use of multiple acetaminophen products (59%), and/or taking too much at one time (34%); on 64% of >4 g days there were two or more deviation types. The odds of >4 g were 4.5 [95% CI 3.1–6.6] times higher on days when both OTC and prescription acetaminophen medicines were taken. Similarly, use of both single-ingredient and combination OTCs increased the odds by 4.0 (2.2–7.2). Use of neither 325 mg nor 500 mg OTC acetaminophen medicines increased the odds of >4 g. Six hundred and fifty milligram extended-release (8-hour) medicines branded for arthritis were associated with increased risk of >4 g (OR = 2.7, 1.4–5.1), partly due to redosing sooner than 8 hours and co-use with prescription medications.

Conclusions: Excess consumption of acetaminophen almost always occurred through deviations from other label directions, suggesting that reinforcement of current directions might reduce over-dosing. Co-use of multiple medication classes increased the risk of over-dosing; warnings to avoid this and aids to identify medications that contain acetaminophen could help. Contrary to hypothesis, the 500 mg OTC formulations were not associated with exceeding 4 g, but 650 mg "arthritis" formulations were associated with exceeding 4 g, due to differential patterns of their use. These findings can inform interventions to reduce over-use of acetaminophen.

12. Prevalence and Correlates of Exceeding the Labeled Maximum Dose of Acetaminophen in the US Adult Population

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Background: Acetaminophen is one of the most commonly used analgesic compounds worldwide, and is contained in hundreds of products; excessive doses can lead to liver damage.

Objectives: Determine the proportion of acetaminophen use that exceeds the label-recommended maximum daily dose of 4 g. Identify correlates of such behavior.

Methods: US adults were recruited from an internet panel in summer 2010; past 30-day acetaminophen users were oversampled. Subjects completed a prospective 7-day diary online on a daily basis. Product names were identified from a comprehensive list; subjects were not required to know that their products contained acetaminophen. An online exit survey elicited attitudes and knowledge related to product ingredients, label reading, and dosing behavior, along with demographics, medical history, and the SF-12 questionnaire on health state. Compared to the US population, there was underrepresentation of low education among the 5,649 respondents who completed the study. The total dose of acetaminophen taken each diary day was calculated based on product names. Attitudinal themes were developed from individual questions by factor analysis. Unconditional logistic regression was used to assess the contribution of multiple variables to the risk of exceeding 4 g in a day.

Results: Among 3,618 acetaminophen users, 163 took >4 g on one or more days (4.5%); the median dose on those days was 5.5 g, and 26 took >8 g (0.7%). >4 g users were characterized by chronic pain, poor physical state, and heavy use of medical care. Knowledge of product ingredients and recommended OTC doses was inversely associated with >4 g use (MVOR, 0.5–0.6), as was the attitude to start with the lowest dose (0.6). The attitude that users could choose their own dose was positively associated (1.3). Reported label reading was not related to >4 g use.

Conclusions: The results have established a baseline of the proportion of acetaminophen use in the US adult population that exceeds the 4 g limit, identified modifiable attitudes and knowledge associated with such use, and characterized subpopulations at high risk.

13. Treatment Patterns and Comorbidities in a Population-Based Cohort of Glioblastoma Patients (pts) Diagnosed 1997–2008

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Background: Glioblastoma multiforme (GBM) is one of the most common, malignant and rapidly progressive forms of brain cancer. Published reports of GBM in non-trial populations are limited.

Objectives: The purpose of this study was to assemble a population-based cohort of GBM pts with comprehensive clinical and demographic information and to define treatment patterns and outcomes in this cohort.

Methods: GBM pts served by Henry Ford Health System (HFHS), a major GBM referral center, were identified using tumor registry ICD-O and histology codes. Eligible pts were newly diagnosed with GBM between 1997 and 2008. Comprehensive data were compiled using tumor registry data (including histology and mortality) with linkages to pharmacy data (including infusion), outpatient and inpatient encounter data, and laboratory results.

Results: Overall, 812 GBM pts were identified; mean age was 54 years (standard deviation 15.8). The cohort was 63% male and 84% white. Among the most common post-diagnosis comorbidities/complications, 14% of pts had venous thromboembolism (95% confidence interval [CI] 12–17), 16% had seizures (95% CI 14–19), and 6% had central nervous system hemorrhage (95% CI 4–7). Arterial thromboembolism occurred in 3% of pts (95% CI 2–4), while 7% experienced infections such as candidiasis, herpes simplex, and pneumocystis pneumonia (95% CI 5–9) and 2% experienced wound dehiscence (95% CI 1–3). 94% (95% CI 93–96) of pts received some form of treatment with 81% undergoing surgery (95% CI 78–84), 75% receiving radiation therapy (95% CI 72–78), and 67% receiving chemotherapy (95% CI 64–70). Median overall survival after diagnosis was 1.4 years (95% CI 1.3–1.5) among all pts, and 1.6 years (95% CI 1.4–2.0) among those diagnosed 2005–2008.

Conclusions: This study presents a well-characterized population-based cohort of GBM pts. Understanding treatment patterns and comorbidities outside the clinical trial setting is important in informing and evaluating real-world treatment decisions. Additional results exploring time trends in systemic cancer therapy and Kaplan-Meier survival curves will be presented.

14. The Rise of Human Papillomavirus (HPV)-Associated Oropharyngeal Cancer (OPC) in Toronto, Canada: A Case for Vaccinating Males

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Background: Although the incidence of OPC has risen over the past two decades compared to other head and neck squamous cell carcinoma (HNSCC), direct linkage to HPV infection as the cause of this rise has not been documented in Canada. HPV testing is not routinely performed in Canada. As a marker for HPV status, clinico-epidemiological factors may act as surrogate factors for the role of HPV infection on the trends of OPC.

Objectives: To assess OPC incidence changes over the last decade as a function of HPV status.

Methods: Medical records of 5,085 HNSCC patients treated at Princess Margaret Hospital, Canada, from 2000 to 2010 were assessed for clinico-epidemiologic factors. HPV status was determined in a subset of patients (2003–2010, by p16 staining). Chi-square and logistic regression models were used.

Results: Of 77% of our OPC patients were male. In analyses of all patients, OPC patients were younger ($p < 0.001$), predominantly male ($p < 0.001$), lighter smokers and drinkers ($p < 0.001$), and had tumors of more advanced stage ($p < 0.0001$) compared to other HNSCCs. When HPV information was known, these associations were often driven by HPV status (e.g., HPV+ OPC patients were younger ($p < 0.0001$), consisted of lighter smokers ($p < 0.0001$), etc. when compared to HPV-negative OPC patients). From 2000 to 2010, the proportion of OPCs increased, but was stable for other HNSCCs ($p < 0.05$). The proportion of node positive disease increased over time in OPC compared to other HNSCC patients ($p = 0.02$). The proportion of heavy smokers declined over time in OPC ($p = 0.003$). In the subset of patients assessed for HPV status, smoking was an important predictor of HPV positivity: 93% of OPC patients who smoked 0–10 pack-years were HPV+, independent of age. When this variable was used as a surrogate for HPV status (in patients with unknown status), the incidence rise in OPC could be attributable to HPV infection.

Conclusions: Using clinico-epidemiological surrogate data in addition to subset assessment of HPV status, the increase of OPC in the past decade was correlated with a rise in HPV-positive tumors. HPV vaccination should be

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considered in young males in addition to females for this reason.

15. Insulin Glargine and Risk of Cancer: A Cohort Study in the French National Healthcare Insurance Database

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Background: A higher risk of cancer in insulin glargine (IG) than in human insulin (HI) users was suspected.

Objectives: To assess the risk of cancer in IG users compared to HI users in the Echantillon Généraliste de Bénéficiaires (EGB) database. Since increased mortality might hide an increased risk of cancer, the combined outcome of death or cancer was also studied.

Methods: The EGB is a representative 1/97th permanent random sample of the national healthcare insurance database that covers approximately 80% of the French population. It includes claims reimbursed since 2003 for approximately 600,000 beneficiaries. The study population was all adults with at least two dispensations of insulin between 1 January 2003 and 30 June 2010, without diagnosis of cancer at the time of first insulin dispensation, or death in the following month, with no more than 1 year without claims. Four cohorts were defined according to incident or prevalent use and whether one insulin was used exclusively or predominantly (≥80% use time). Cox proportional hazards time-dependent models stratified on the propensity score quartiles for use of IG vs. HI, and adjusted on insulin, biguanide and sulfonylurea possession rates, were used to assess the risk of cancer and death or cancer.

Results: Only patients with type 2 diabetes were analysed, because there was only one cancer among incident type 1 diabetes. Exposures varied from 2,273 to 614 patient-years for incident exclusive IG or HI users respectively, and from 3,125 to 2,341 patient-years for all predominant IG or HI users. All-type cancer hazard ratios (HR) with IG vs. HI ranged from 0.59 (95% CI: 0.28–1.25) in incident exclusive users to 0.58 (95% CI: 0.34–1.01) in all predominant users. Cancer risk increased with exposure to insulin or sulfonylureas in these patients. Adjusted HR for death or cancer associated with IG compared to HI ranged from 0.58 (95% CI: 0.32–1.06) to 0.56 (95% CI: 0.36–0.87).

Conclusions: There was no excess risk of cancer in type 2 diabetic patients on IG alone compared to HI alone. The overall risk of death or cancer in patients on IG was about half that of patients on HI, thereby excluding bias from competing risk of death.

16. The Validity of Prescription and Other Health Service Claims and Self-Report in Identifying Cases of Invasive Breast Cancer in Australia

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Background: Routinely-collected and self-reported health data are increasingly being used to identify health status and service use. Australian state-based cancer registries are the "gold standard" for identifying breast cancer, but researchers working with other datasets (i.e., prescription claims) may need to identify cases without linkage to these registries.

Objectives: To determine the validity of prescription claims for selective estrogen receptor modulators (SERM) and aromatase inhibitors (AI), hospital procedures, claims for outpatient procedures and radiotherapy, and self-report in identifying cases of invasive breast cancer in Australia against the Cancer Registry.

Methods: Invasive breast cancers recorded on the Cancer Register between 2004 and 2008 for women in the New South Wales 4*5 and Up Study* were compared with cases identified by: (1) SERM and AI prescription claims and (2) outpatient procedures and radiotherapy from 2004 to 2009; (3) NSW Admitted Patients Data Collection (hospital records) between July 2004–February 2009; and self-reported diagnosis of breast cancer between 2003 and 2009 in the *45 and Up Study* baseline survey. Sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated for each dataset compared with the Cancer Registry.

Results: Of 143,010 women in the *45 and Up* cohort, 2,661 (1.9%) had breast cancer recorded on the registry. Sensitivity for self-report of breast cancer diagnosis was 73.0%, with hospital records, PBS and MBS claims data being 86.4%, 65.7% and 58.0%, respectively. PPV was highest for hospital (84.0%) and MBS data (80.4%) and lower for self-report (40.9%) and PBS claims (49.4%). Specificity and NPV were >99% for all comparison datasets evaluated.

Conclusions: In the absence of cancer registrations, cases of breast cancer were most accurately detected using hospital records, and to a lesser extent self-report. Prescription and outpatient claims had only moderate sensitivity and/or PPV, likely reflecting that not all patients have

post-surgical pharmacological or medical treatment. However, all of the datasets accurately identified cases without breast cancer, so are suitable for researchers wishing to exclude breast cancer cases from their data.

17. Futile Drug Use at the End of Life? Continuation of Statins after a Cancer Diagnosis

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Background: Despite the large body of evidence guiding the initiation of drugs to manage comorbid disease there is little guidance on ceasing medications at the end of life. However, evidence suggests that drugs used for the secondary prevention of comorbid conditions are continued longer than clinically necessary.

Objectives: To examine statin discontinuation rates in a cohort of elderly Australians with newly diagnosed cancer using population-based secondary health data.

Methods: Observational cohort study of Department of Veterans' Affairs clients aged ≥65 years. Cancer patients were diagnosed between 2005 and 2007, alive for at least 6 month after diagnosis and had evidence of statin use in the 90 days prior to diagnosis (n = 1,731). They were age and sex matched to 3,462 non-cancer patients prescribed statins in the same period. We compared statin discontinuation rates up to 4 years post-diagnosis and examined the factors associated with discontinuation.

Results: The cancer cohort discontinued statins at a significantly higher rate than the comparison cohort at 3, 6 and 12 months of follow-up (9.7% vs. 7.4% at 12 months, respectively) but discontinuation rates were comparable at 4 years (27%). More than 20% of the cancer cohort with metastatic disease at diagnosis and 35% with localized disease at diagnosis were dispensed a statin within 30 days of death. Cancer patients with metastatic disease at diagnosis (aHR 3.9, 95% CI 2.72–5.59), older age (aHR 0.85, 95% CI 0.76–0.95), upper gastro-intestinal organs and liver cancer (aHR 2.95, 95% CI 1.92–4.53) and lung cancer (aHR 1.99, 95% CI 1.32–3.00) were more likely to discontinue statin therapy.

Conclusions: Cancer patients would benefit from a comprehensive reassessment of all drug treatments. The original therapeutic goals of primary and secondary prevention of other diseases may be largely futile in light of a limited prognosis.

18. The Associations between Treatment Interruption/Nonadherence to Tamoxifen and Mortality of Breast Cancer Patients: A Population Claim-Based Data Analysis in Taiwan

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Background: Long-term daily oral adjuvant hormonal therapy (HT) has been proved in trials to significantly reduce risk of recurrence and improve survival of hormone-sensitive breast cancer. However, the rates of treatment interruption and nonadherence to tamoxifen (TAM) are found high in practice and may lead to poor clinical outcomes.

Objectives: This study aims to explore the associations between the treatment interruption/nonadherence of TAM and the mortality of Taiwanese breast cancer women.

Methods: This study was conducted by using the Taiwan Health Insurance Research Database from 1999 to 2008. Newly diagnosed female breast cancer patients with TAM as initial HT were identified along with their TAM prescriptions. Treatment interruption was defined as over 180 days between two prescription coverage. The medication possession ratio (MPR) was dichotomized by 80%. Hazard ratios (HR) of treatment interruption and nonadherence (MPR < 80%) in mortality were estimated by Cox regression with additional covariates of age, cancer initial therapy, income related insurance payment, and comorbidity.

Results: Of the 35,413 patients, the median follow-up time was 52 months. There were 5,360 (15.1%) with at least one TAM treatment interruption, and 15,835 (44.7%) with poor adherence to TAM (MPR < 80%). The Kaplan-Meier estimates indicated 5-year survival rate was 87.4% and 84.9% in patients persisted and interrupted TAM (Log rank, $p < 0.0001$), 88.8% and 84.3% in patients adhered and nonadhered to TAM, respectively (Log rank, $p < 0.0001$). Treatment interruption (adjusted HR: 1.56; 95% CI: 1.45–1.69, $p < 0.0001$) and nonadherence to TAM (adjusted HR: 1.14; 95% CI: 1.07–1.22, $p < 0.0001$) were found significantly associated with all-cause mortality.

Conclusions: Treatment interruption and poor adherence of TAM are associated with mortality. Future studies need to include aromatase inhibitors to evaluate the association between nonadherence to HT and breast cancer

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related mortality. To improve breast cancer treatment outcomes, it is vital to ensure adherence of TAM therapy.

19. The Impact of Unmeasured Confounders in Cardiovascular Studies Performed in Administrative Databases

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Background: Administrative databases are increasingly being used in pharmacoepidemiology. However, given that important confounders are often missing in these databases such as smoking, body mass index, and other clinical variables, and that they are seldom truly population-based, studies using them are often criticized.

Objectives: The aim of our study was to estimate the impact of unmeasured confounders in the association between antihypertensive (AH) and statin drug use and the risk of cardiac events, stratified on patient socio-demographic status and gender.

Methods: Data were obtained from two administrative databases from Quebec (RAMQ and Med-Echo) and a mailed auto-administered questionnaire. Estimates of bias for six potential confounders (obesity, physical activities, smoking, alcohol, income and cardiovascular family history) were calculated using the method proposed by Schneeweiss for three different study populations (workers, welfare recipients, and elderly), stratified by gender. Estimates of bias were calculated for each confounder individually as well as for all confounders combined.

Results: Of 6,453 subjects returned their questionnaire, and were included in this study. We found that the bias for the non-adjustment of these six potential confounders was different for males and females in each study population. The combined bias was -4.2% and -0.7% for male and female workers, respectively, meaning that non-adjustment would lead to an underestimation of the association between AH/statin use and the risk of cardiac events. Similar gender differences in bias estimates were observed in the other study populations.

Conclusions: We have shown that unmeasured confounders can have a significant impact on risk estimates. The impact is dependant on patient gender.

20. Comparison of Five Diagnosis Based Comorbidity Measures in Predicting Health-Related Quality of Life (HRQoL) in Multiple Sclerosis Patients

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Background: Prior comorbidity measures were developed to predict hospitalization, mortality and expenditure. Recently in 2011, a comorbidity measure was developed to predict health-related quality of life (HRQoL).

Objectives: To compare the performance of Charlson/D'hoore (CCI), Elixhauser (ECI), Elixhauser-point scale (ECI-P), combined comorbidity index (CCI + ECI) and HRQoL-comorbidity index (HRQoL-CI) in predicting HRQoL in Multiple Sclerosis (MS) patients.

Methods: A retrospective cross-sectional study was performed using 2002 to 2009 Medical Expenditure Panel Survey (MEPS) data, a national probability sample survey of the civilian non-institutionalized U.S. population. The study included all patients diagnosed with MS. International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and clinical classification codes were used to create five comorbidity measures. HRQoL is documented in MEPS using short form health survey (SF-12), with physical component score (PCS) and mental component score (MCS). Ten linear regression analyses models were constructed: five for PCS and MCS each. Age, race and sex were included as baseline variables in all models while incorporating CCI, ECI, ECI-P, CCI + ECI and HRQoL – CI measures one at a time. Adjusted R^2 were compared to assess the comparative performances of comorbidity measures. All analyses were adjusted for complex survey design.

Results: An estimated of 4.9 million patients had MS. The mean age was 49 ± 12 years, with 82.93% non-Hispanic whites. The average PCS and MCS for MS patients were 44.47 ± 12.17 and 33.82 ± 12.28, respectively. ECI (R^2 = 0.22) outperformed CCI (R^2 = 0.16), ECI-P (R^2 = 0.07), ECI + ECI (R^2 = 0.18) and HRQoL-CI (R^2 = 0.21) in predicting PCS. Likewise, ECI (R^2 = 0.26) outperformed CCI (R^2 = 0.14), ECI-P (R^2 = 0.03), ECI + ECI (R^2 = 0.18) and HRQoL-CI (R^2 = 0.24) in predicting MCS.

Conclusions: Even though Elixhauser comorbidity index was not developed to predict HRQoL, it outperformed the HRQoL-CI for both PCS and MCS dimensions of HRQoL. Elixhauser comorbidity index may be a better risk adjustment tool for studies involving HRQoL as an outcome.

21. Combining Data in Multi-Country Studies: Mega-Analysis vs. Meta-Analysis

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Background: Over the past years, an increasing number of multi-country pharmacoepidemiological studies have been performed. However, there is limited knowledge on statistical methods to combine data from individual databases.

Objectives: To evaluate the difference between an individual patient mega-analysis and a traditional meta-analysis when combining data from two pharmacoepidemiological studies. They evaluated the risk of hip fracture in patients with multiple sclerosis (MS).

Methods: We have previously estimated the risk of hip fracture in incident MS patients vs. population-based controls using the UK General Practice Research Database (GPRD). There was an almost threefold increased risk of hip fracture (adjusted hazard ratio (adj HR) 2.8 [95% CI 1.8–4.3]). However, when we studied risk of hip fracture in incident MS patients in the Danish national databases, fracture risk was not significantly increased: adj HR 1.8 (0.9–3.5). In the present study, we investigated whether the different study results between the GPRD and the Danish study could be explained by differences in patient characteristics, calendar time, duration of follow-up or confounders. Secondly, we investigated whether an inverse-variance fixed effect meta-analysis of the two studies provided different results than an individual patient mega-analysis, in which the differences between the study characteristics were reduced as much as possible.

Results: A meta-analysis of the two original studies yielded an adj HR of 2.5 (95% CI 1.7–3.5). When we made the two study populations comparable in terms of calendar time, age at index date (so equal proportion of incident/prevalent patients), duration of follow-up and confounders, we found an adj HR of hip fracture with MS of 2.7 (1.6–4.6) in GPRD and an adj HR of 3.4 (2.7–4.3) in Denmark. An individual patient mega-analysis of these study populations with comparable characteristics resulted in adj HR 3.3 (2.7–4.1), which was 34% higher than the estimate from the meta-analysis.

Conclusions: Individual choices in study design and the nature of different pharmacoepidemiological databases may explain substantial amounts of heterogeneity when data from multi-country studies are combined.

22. Design Aspects of Pharmacoepidemiological Two-Phase Studies

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Background: Two-phase designs for case-control studies or time-to-event data can be used for pharmacoepidemiological database studies if confounder information is missing in the database (phase 1) but is available in a validation subsample (phase 2). Bias and efficiency of parameter estimates depend particularly on the sampling strategy and the stratification used in the analysis.

Objectives: To compare sampling strategies and stratifications with respect to bias and efficiency of parameter estimates in a simulation study of realistic pharmacoepidemiological two-phase studies.

Methods: We conducted a simulation study mimicking the two-phase study of Behr et al. (2012, DOI 10.1002/pds.3193) on the risk of bleeding associated with phenprocoumon use. The estimated disease model and covariate structure were used to simulate 1,000 phase 1 data sets with 26,208 patients each. We adopted six sampling strategies to draw subsamples of sizes 500, 1,000, 2,000, and 10,000 from each phase 1 sample. Each subsample was enriched with covariates that were not available in the phase 1 data. Phase 1 and 2 samples were analyzed with two-phase methods using six stratifications. Simple strategies and stratifications considered only few important covariates (e.g., sex or age), whereas complex ones employed a disease score based on multiple covariates. The simulated two-phase studies were evaluated with respect to bias and efficiency of parameter estimates.

Results: Non-representative sampling of covariates led to biased estimates if the respective covariates were ignored in the stratification used in the two-phase analysis. Including information on the rare exposure phenprocoumon in the sampling strategy considerably increased the efficiency of that risk estimate. Stratifications based on a disease score showed little effect on efficiency, whereas stratifications including single covariates directly performed well for these covariates. Oversampling of older patients improved the efficiency of estimates for several covariates.

Conclusions: Properly designed two-phase studies can reduce bias and improve efficiency of several parameter estimates in a multivariable model. However, the design should concentrate on important or rare covariates.

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23. Use of Claims Data to Predict Dependence in Older Adults

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Background: Estimating drug effectiveness among older adults in non-experimental population-based studies has been hampered by unmeasured confounding due to frailty. Predicting dependence, a proxy for frailty, may improve confounding control.

Objectives: To identify predictors of dependence in activities of daily living (ADL) in a representative sample of Medicare beneficiaries.

Methods: We included only community-dwelling respondents to the 2006 Medicare Current Beneficiary Survey, ≥65 years old, with Medicare Part A, B, home health, and hospice claims for 8 months prior to the fall interview. ADL dependence (ADL-D) was defined as needing help with bathing, eating, walking, dressing, toileting, or transferring. Potential predictors were demographics and diagnoses (ICD-9) associated with claims for high-risk conditions (e.g., falls, hip fracture, and dementia). We used multivariable logistic regression to predict ADL-D and to estimate odds ratios (OR) and 95% confidence intervals (CI).

Results: Of 6,035 respondents, 58% were female, 88% white with an average age of 77 (SD: 7.3) years and an ADL-D prevalence of 9.7% (N = 590). The strongest predictors of ADL-D were amputation (OR = 12.8, CI: 4.9–34), aspiration pneumonia (OR = 3.4, CI: 1.3–9.2), paralysis (OR = 3.3, CI: 1.7–6.2), and oxygen dependence (OR = 2.9, CI: 1.4–6.0). Less likely to be ADL dependent were those screened for cancer (OR = 0.45, CI: 0.36, 0.58) or treated for vertigo (OR = 0.61, CI: 0.46–0.82). The final model had a c-statistic of 0.83 and also included dementia (OR = 2.2), psychiatric disease (OR = 1.7), heart failure (OR = 1.9), vertebral fracture (OR = 2.1), hip fracture (OR = 1.7), bladder dysfunction (OR = 1.6), stroke (OR = 1.8), serious infection (OR = 1.5), weakness (OR = 1.6), and difficulty walking (OR = 1.6), as well as age (OR = 1.1 per year increase) and non-white race (OR = 1.7) .

Conclusions: This study shows that claims data can be used to predict dependence in ADLs. Our finding has important implications for controlling for confounding in population-based studies of drug effectiveness in older adults.

24. Automated Identification of Asthma Patients within an Electronical Medical Record Database Using Machine Learning

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Background: New initiatives such as Sentinel and OMOP promote the merged use of electronic medical record (EMR) databases to increase the sample size. A key challenge for use of these huge databases is disease validation. The conventional method of manual chart review is labor intensive, often non-systematic and inefficient. One strategy to address this problem is to use machine learning tools to identify cases.

Objectives: To investigate and evaluate the performance of a machine learning approach to identify children with asthma in a huge EMR database, including free text, disease codes and prescriptions of asthma drugs.

Methods: From the IPCI (Integrated Primary Care Information) database, a Dutch GP database containing the complete medical records of more than 1 million patients, all potential asthma patients, aged 6–18 years between 2000 and 2011, were identified with a broad automated search on ICPC asthma disease codes, free text and asthma drug prescriptions. First, a random sample (n = 5,039) of all potential cases (n = 64,327) was manually reviewed by 2 medical doctors and categorized according to a predefined algorithm. Second, based on this sample set machine learning (ML) was used to automatically generate decision trees for case identification. Training and testing was done by fivefold cross validation.

Results: The sample set consisted of 6% definite, 24% probable, 2% doubtful cases and 68% non cases. Depending on the sampling strategy used, the positive predictive value (PPV) ranged from 0.11 to 0.26, sensitivity (Sn) from 0.57 to 0.94 and specificity (Sp) from 0.52 to 0.89 for definite cases (asthma diagnosed by specialist). For probable cases (asthma diagnosed by GP) PPV ranged from 0.49 to 0.51, Sn from 0.84 to 0.86 and Sp from 0.69 to 0.73.

Conclusions: Our results demonstrate that ML to automate identification of cases in huge EMR databases performs reasonably well. The optimal ML sampling strategy depends on the research question e.g., incidence/prevalence studies require a method with a large sensitivity and have to compromise on specificity, while outcome studies require a method with a large specificity.

25. Clarithromycin Use in Early Pregnancy and the Risk of Miscarriage – A Register Based Nationwide Cohort Study

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Background: The macrolide clarithromycin has been associated with fetal loss in animals and a study has found a doubling in the frequency of miscarriages among women using clarithromycin in early pregnancy. These results are though inconclusive.

Objectives: The aim of the study was to investigate whether clarithromycin use in early pregnancy was associated with miscarriages.

Methods: We conducted a nationwide cohort study including all women in Denmark with a known conception between 1997 and 2006. The Fertility Database was used to identify all women giving birth and the National Hospital Register was used to identify all women with a record of a miscarriage or induced abortion. Prescription data was obtained from the National Prescription Register. The primary outcome was the number of miscarriages among users of clarithromycin compared to non-users. Cox proportional hazard regression analysis was used to estimate the hazard of miscarriage.

Results: We identified 934,840 pregnancies (705,837 live births, 80,889 miscarriages, and 148,114 induced abortions) in the study period. Four hundred and one women redeemed a prescription of clarithromycin in the first trimester of which 40 (10%) experienced a miscarriage. The hazard ratio (HR) of having a miscarriage after exposure to clarithromycin compared to unexposed was 1.66 (95% CI 1.22–2.26). When adjusting for maternal age, income, education, and the number of prior miscarriages the HR was 1.56 (95% CI 1.14–2.13). In order to analyse the causal inference we estimated the average causal effects in a propensity score-matched model and found HR to be similar (1.71 [95% CI 1.20–2.45]). To analyze for confounding by indication we investigated and found no increased hazard of having a miscarriage when redeeming a prescription of penicillin (HR = 1.02 [95% CI 0.98–1.07]), erythromycin (HR = 1.00 [95% CI 0.92–1.10]) or amoxicillin (HR = 0.97 [95% CI 0.87–1.08]) in the first trimester.

Conclusions: There is an increase in the prevalence of miscarriages among women redeeming a prescription of clarithromycin in early pregnancy. This is supported by previous studies in both animals and humans.

26. Drug Utilization among Pregnant Diabetic Women in US Managed Care

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Background: Type 2 diabetes mellitus (T2DM) carries substantial health risks for both mother and child, creating concern as T2DM prevalence among young women is increasing.

Objectives: To examine anti-diabetic drug utilization among T2DM pregnant women.

Methods: We used IMS LifeLink, including claims data of 104 US managed care health plans, to establish a retrospective cohort of pregnant women, age 18–46 years (N = 96,740) with Current Procedural Terminology (CPT) codes for a live birth and a 15 months eligibility period before and 3 month eligibility after delivery. T2DM was identified based on ≥2 in – or outpatient claims with ICD-9-CM 250X0 or 250x2 and ≥1 drug claim for an anti-diabetic drug before pregnancy. We evaluated the prevalence of anti-diabetic drug use before, during and after pregnancy, and respective secular trends across the study period (1999–2009), using chi-square test and linear regression.

Results: Of 4.2% (n = 4,043) of the cohort had T2DM before pregnancy. Over the course of the study, 12.5% (1999) to 48.5% (2009) of DM women received AD drugs before pregnancy ($p < 0.0001$), increasing to 36.3% (1999) and 69% (2009) ($p < 0.0001$) during pregnancy. The yearly prevalence of insulin increased from 28% to 29% in 1999–2009 ($p = 0.0771$), while sulfonylureas and metformin use increased from 2.5% and 3.8% (1999) to 18.8% and 16.8% (2009) ($p < 0.0001$) during pregnancy. The most common anti-diabetic drugs during pregnancy were thiazolidinediones (TZD), sulfonylureas, metformin, and insulin. Insulin and sulfonylureas steadily increased in prevalence from the 1st to 3rd trimester, while metformin and TZD decreased.

Conclusions: Insulin usage increased from the 1st to 3rd trimester. Metformin has increased in prevalence across years, but decreases in usage as pregnancy progresses. Sulfonylureas have increased in utilization both in pregnancy and over the study time period. The utilization of oral anti-diabetic medications during pregnancy demonstrates the need for additional evidence regarding teratogenicity and maternal outcomes.

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27. Pregnancy Outcomes in Women Dispensed Ondansetron in Pregnancy

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Background: Ondansetron is most commonly used for the treatment of nausea and vomiting arising from cancer therapies, or for post-operative nausea. There is limited data on the safety of ondansetron for use in pregnancy.

Objectives: To describe the women dispensed ondansetron in pregnancy and their birth outcomes.

Methods: This was a population-based study using the data linkage capacity in Western Australia (WA). Records were extracted from five state health datasets, including the WA Register of Developmental Anomalies, and dispensing data from the national Pharmaceutical Benefits Scheme. The cases were all births in WA from 2002 to 2005 where the mother was dispensed ondansetron (N = 251 pregnancies, 263 children). The controls were all other pregnancies during the same period (N = 96,447 pregnancies, 98,062 children). Maternal socio-demographic characteristics, pregnancy and delivery information were included as well as birth outcomes such as birth defects, birth weight and length, and gestational age.

Results: There were 251 pregnancies where the women were dispensed ondansetron, 204 during the first trimester. When compared with all other pregnant women, these women were less likely to smoke during their pregnancy (OR 2.9; 95% CI 1.7–4.7), and more likely to have a multiple birth (2.7; 1.5–5.0), to deliver preterm (1.8; 1.2–2.5), to have an elective Caesarean delivery (2.0; 1.5–2.6), to have used fertility treatment (1.8; 1.0–3.4), to live in a higher socio-economic area (t-test, $p < 0.0001$), and to have an obstetrician deliver their child (3.9; 2.9–5.1). Their children were more likely to have a lower birth weight and birth length. We did not find an increased risk for any category of major birth defects with first trimester exposure (1.1; 0.6–2.0), N = 10/211; 4.7% cf. 4.1%. Although the numbers of affected children were small, there was an increased risk of "753.2 Obstructive defects of renal pelvis and ureter" (7.2; 2.3–22.8).

Conclusions: This population-based study is one of the largest cohorts of pregnant women dispensed ondansetron in pregnancy. It provides a profile of the women and their pregnancy outcomes. It is reassuring that there does not appear to be an increased risk of major birth defects.

28. TNFα Therapies during Pregnancy and Birth Outcomes: A Nordic Population-Based Study

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Background: Chronic inflammatory diseases may be associated with adverse birth outcomes. Several anti-tumor necrosis factor alpha (TNFα) therapies have been introduced and, while discouraged, may be prescribed during pregnancy. Data regarding their impact on birth outcomes are limited.

Objectives: To assess associations between TNFα therapies during pregnancy and preterm birth, growth restriction, major congenital anomalies and infections during infancy.

Methods: From the birth registers in Denmark, Finland and Sweden we indentified infants born from 2000 to 2009. Mothers exposed to TNFα therapies during pregnancy were identified from drug registers and the disease-specific ARTIS register in Sweden and the RobFin register in Finland. Unexposed mothers with rheumatoid arthritis, ankylosing spondylitis, psoriasis or inflammatory bowel disease constituted the comparison group. Information on birth outcomes, congenital anomalies and infections was obtained from the birth, patient and drug registers. Associations were assessed by exact logistic regression analyses, conditioned on country of birth and maternal disease. We present adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

Results: We identified 318 mothers exposed to TNFα therapy and 35,903 unexposed mothers. The exposed mothers were older, more often primiparous, less often smokers and had a lower body mass index. Exposure to TNFα therapies was associated with preterm (OR 1.91, 95% CI: 1.38–2.61) and small for gestational age birth (OR 2.00, 95% CI: 1.11–3.38). Of the 305 infants exposed before the 2nd trimester, 11 (3.6%) were born with a major congenital anomaly (OR 0.81, 95% CI: 0.40–1.49). Risks were not increased for infection-related hospitalizations during infancy (OR 1.03, 95% CI: 0.70–1.47) nor for having antibiotics dispensed during infancy (OR 0.82, 95% CI: 0.62–1.09).

Conclusions: Infants exposed to TNFα therapies in utero were more often born preterm and small for gestational age. We found no increased risks of major congenital anomalies or infections during infancy. Uncontrolled confounding, such as disease severity,

might explain the increased risks of preterm birth and growth restriction.

29. Inflammatory Bowel Disease in Pregnancy and Thrombophilic Disorders – Impact of Type of Disease and Treatment

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Background: Inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis, occurs in 0.5% of women who give birth. IBD during pregnancy is associated with increased risks of venous thromboembolism (VTE) and placenta-mediated complications, such as hemorrhage, are more common in thrombophilic women. IBD therapy during pregnancy may affect risks of thrombophilic disorders.

Objectives: To assess risks of VTE and antenatal hemorrhage in pregnant women with Crohn's disease and ulcerative colitis by treatment.

Methods: We included 2,161 women with IBD and 10,605 healthy controls, matched by age and parity, among women who gave birth in Sweden between October 2006 and December 2009. Information was obtained from the National Health Registers. IBD women were categorized as: (1) no drug exposure or clinical events, (2) maintenance therapy and (3) corticosteroids, surgery or admission to hospital because of flaring disease. Risks are presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Adjustments were made for age, parity, smoking status and comorbidity.

Results: Women with Crohn's disease had increased risks of antenatal hemorrhage (OR 1.80, CI: 1.27–2.46), with the highest risk (OR 2.21, CI: 1.39–3.51) among those with no drug exposure or clinical events. Women with ulcerative colitis had increased risks of thromboembolism (OR 3.75, CI: 1.51–9.31), with a rising trend across treatment groups. Women who experienced flares during pregnancy had the highest risks (OR 8.48, CI: 1.73–41.7).

Conclusions: The increased risks of antenatal hemorrhage in women with Crohn's disease, contrast the increased risks of VTE in women with ulcerative colitis. Thus, thrombophilic disorders and the impact of treatment may present differently in pregnant women with Crohn's disease and ulcerative colitis.

30. Microtia: Findings Suggest No Association with Vasoactive Medications

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Background: Little is known about the etiology of microtia, an external ear malformation that varies in presentation from minor changes in size or structure to absence of the external ear and auditory canal (anotia). Causal mechanisms hypothesized include vascular disruption and alteration in neural crest cell migration.

Objectives: To investigate possible markers of vascular disruption.

Methods: We analyzed data from the US National Birth Defects Prevention Study (NBDPS), a population-based case-control study that interviews women in 10 states within 2 years of delivery. A clinician reviews medical records of cases; infants with chromosomal abnormalities and syndromes of known etiology are excluded. For this study of deliveries between 1997 and 2005, 409 microtia cases, with or without additional defects, were compared to 6,560 nonmalformed controls. Exposures studied included vasoactive medications (primarily antihypertensives, bronchodilators, decongestants, NSAIDs) and smoking from 1 month preconception through the first trimester and markers of vascular events (diabetes, hypertension, multiple gestation). We calculated adjusted odds ratios and 95% confidence intervals (OR; 95% CI) using multivariable logistic regression.

Results: Risks were not appreciably increased for vasoactive medications, smoking, and hypertension; where estimates were stable, ORs ranged from 1.0 to 1.2. We observed an increase in risk for multiple compared to singleton births (OR: 2.5; 95% CI: 1.5, 4.2). Of note, while the risk estimate for gestational diabetes was slightly increased (1.4; 1.0, 2.0), the estimate for Type 1 or Type 2 diabetes diagnosed before or during the index pregnancy was larger (7.2; 4.0, 13.2). Further, in a sub-analysis that explored the combination of NSAID use and diabetes (Type 1/2 and gestational), the risk estimates for NSAIDs alone and diabetes alone were 1.2 (0.9, 1.5) and 1.7 (1.2, 2.5), respectively, compared to 3.0 (1.8, 5.1) for those with both exposures.

Conclusions: The findings suggest that microtia may be part of a diabetic embryopathy rather than a manifestation of vascular disruption. The possible role of NSAIDs in this mechanism should be explored further.

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31. The Clinical and Economic Costs Associated with Elevated Triglyceride Levels

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Background: High levels of triglycerides (TG) are associated with increased rates of pancreatitis, diabetes, cardiovascular (CV) events, and chronic kidney disease (CKD). However, little is known about how the incidence rates and associated costs of these conditions varies across the different categories of TG levels that are outlined by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines.

Objectives: To estimate the clinical and economic costs among individuals in each TG category (normal: <150 mg/dL; borderline high: 150–199 mg/dL; high (HTG); 200–499 mg/dL; and severe hypertriglyceridemia (SHTG): ≥500 mg/dL).

Methods: Utilizing two large US healthcare claims databases, we identified 4,266,538 adults in the US between June 2001 and December 2010, who maintained continuous enrollment with medical and pharmacy claims for ≥6 months before their index TG lab value. We developed Cox proportional hazards models to estimate the incidence rates associated with the aforementioned outcomes among patients in each TG category. We also quantified the all-cause and CV-related utilization outcomes using negative binomial regression models and constructed generalized linear models to evaluate predicted costs (including all-cause and CV-related medical and pharmacy costs) within these four TG categories.

Results: Using SHTG adults as the reference, we found decreasing trends in the incidence rates and utilization models associated with all four of the clinical events across the TG categories. A similar pattern was observed in the economic models. Specifically, the total all-cause medical costs for individuals per year with SHTG, HTG, borderline HTG, and normal TG levels were $9,502, $8,370, $7,809, and $7,100, respectively. The total CV-related costs within these same TG categories per individual per year were $3,000, $2,145, $1,818, and $1,467, respectively.

Conclusions: These findings provide evidence supporting the association between elevated triglycerides and an increased risk of clinical events. This increased risk translates into substantial differences in annual healthcare utilization and costs per individual.

32. Development of a Model Predicting the Medico-Economic Impact of Telemonitoring for Patients with Heart Failure in France

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Background: Heart Failure (HF) is a serious condition associated with frequent hospitalizations. Telemonitoring (TM) can improve HF management and reduce all-cause mortality, HF-related hospitalizations and related costs.

Objectives: A model was developed to predict the effect of TM on HF-hospitalizations and survival in HF patients in France.

Methods: A Markov modeling approach was used to simulate HF progression, with TM compared to usual care, over a 2-year time horizon. The number of hospitalizations was considered as an indicator of disease progression. The model assumes that TM alerts can prevent transitions to health states with increased risk of HF decompensation. The effectiveness of TM in preventing HF-hospitalizations and all-cause mortality was based on published meta-analyses, and input data on literature and French hospital statistics. Deterministic and probabilistic sensitivity analyses were performed to assess uncertainty around results.

Results: The model predicted that patients would survive on average for 1.5 years after the 1st hospitalization for HF decompensation, with 3.3 hospitalizations over a 2-year time horizon. TM would increase life-expectancy by 0.9 months (corresponding to a reduction rate of 16.4% in mortality), and would save 0.6 hospitalizations per patient over 2 years (corresponding to a reduction of 6 days spent in hospital and a reduction rate of 18.1% in hospitalization). Providing TM to 1,000 new HF patients per year, after 1st hospitalization, would avoid approximately 590 hospitalizations over 2 years and save 1.3 m€ per year (2,009 average cost for HF-related hospitalization in France = 4,455€).

Conclusions: The predicted numbers of HF-hospitalizations avoided and improvements of life-expectancy over a 2-year period support further investigations aiming to develop TM for HF patients. The model predictions appear consistent with data from the literature, but we recommend updating it using information collected through a TM program when implemented in clinical practice.

33. Are Vasodilators of Value in the Care of Patients Hospitalized for Acute Heart Failure?

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Background: Despite limited evidence, guidelines recommend the use of IV vasodilators in addition to diuretics for the treatment of acute heart failure (AHF) patients (pts) who are not hypotensive.

Objectives: To investigate whether pts hospitalized for AHF and treated with IV loop diuretics in combination with IV nitrates (NT) or IV nesiritide (NES) achieve better outcomes compared to those receiving diuretics alone.

Methods: U.S. hospital records (2007–2009) from the Marketscan Hospital Drug Database were analyzed to identify pts' first observed hospitalization with a primary diagnosis of AHF. Pts < 18 years old, with hypotension, cardiogenic shock, myocardial infarction, and acute coronary syndromes were excluded. Pts receiving diuretics were matched pair-wise with pts receiving diuretics + NT or diuretics + NES using the propensity score method. Outcomes included in-hospital mortality, hospital length of stay (LoS), and costs during the first AHF hospitalization.

Results: Of 4,401 diuretic vs. diuretic + NT matched pairs (mean age 70.1 years, 49% male) and 2,254 diuretic vs. diuretic + NES matched pairs (mean age 70.4 years, 59% male) were identified. Diuretic + NT and diuretic + NES pts had longer LoS (7.3 and 7.9 days, respectively) vs. diuretic pts (5.7 and 5.8 days for corresponding pairs; $p < 0.01$). LoS in ICU was about 0.7 days longer ($p < 0.01$) in both vasodilator cohorts vs. diuretics alone. Mortality was similar between diuretic and diuretic + NT pts (1.9% vs. 2.0%; $p = 0.88$) but higher among diuretic + NES pts (2.2% vs. 3.1%; $p = 0.05$). Hospitalization costs were significantly greater in both vasodilator cohorts (diuretics: $8,949 vs. diuretics + NT: $14,016, $p < 0.01$; diuretics: $9,057 vs. diuretics + NES: $14,210, $p < 0.01$).

Conclusions: This real-world study of pts hospitalized for AHF indicates that neither NT nor NES in addition to diuretics improve survival compared to diuretics alone, and are associated with both longer LoS (> 1.5 days) and higher (57%) hospitalization costs. These data raise the question as to whether currently available IV vasodilators utilized to treat pts hospitalized for AHF are of value in reducing in-hospital mortality, LoS, and costs.

34. Comparative Cost-Effectiveness of Interventions to Improve Medication Adherence after Myocardial Infarction

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Background: Non-adherence to secondary prevention medications after myocardial infarction (MI) is extremely common and contributes to poor health outcomes and excess spending. Adherence may be improved in a variety of ways, yet little is known about the relative costs and effectiveness of these strategies.

Objectives: To evaluate the cost-effectiveness of interventions intended to improve adherence to secondary prevention medications among post-MI patients.

Methods: We developed a Markov state-transition model to evaluate five strategies for improving adherence to secondary prevention medications after hospital discharge for MI: (1) mailed education; (2) blister packaging; (3) polypill; (4) disease management; and (5) usual care. The main outcome measure was the incremental cost-effectiveness ratio (ICER) of each intervention compared to usual care as measured in dollars per quality-adjusted life year (QALY) gained. Parameter estimates were derived from clinical trials and other published sources. The analysis was performed from a societal perspective over a lifetime horizon and assumed a discount rate of 3% per year.

Results: Compared with usual care, only mailed education both improved health outcomes and reduced spending. The added cost of the polypill, disease management, and blister packaging were $110,500, $148,100, and $422,900 per QALY, respectively. The results were robust to alterations in model parameters although the polypill strategy became increasingly cost-effective at lower drug prices, higher adherence, and under an assumption that its therapeutic effect is equivalent to that of the individual drug components. For example, at a cost-effectiveness threshold of $100,000 per QALY, the polypill strategy would be preferred over usual care if the monthly price of the polypill decreased to $164 and would become cost-saving at a price of < $84 per month.

Conclusions: Mailed education may be a cost-saving strategy for improving post-myocardial infarction medication adherence. The polypill approach could also be cost-effective under favorable assumptions about its price, adherence, and therapeutic effectiveness.

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35. Impact of Full Coverage for Preventive Medications after Myocardial Infarction on the Time Course of Adherence

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Background: Adherence to medications that are prescribed after myocardial infarction is poor. The MI-FREEE Trial evaluated whether elimination of out-of-pocket costs would increase adherence and improve outcomes (NK Choudhry et al. N Engl J Med 2011).

Objectives: We evaluated the short and long-term impact of randomization to full prescription coverage on the course of adherence to the three targeted drug classes (statins, beta-blockers [BB], and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers [ACE/ARB]), and a referent drug class (clopidogrel) with prescription coverage unaffected by the intervention.

Methods: We enrolled patients discharged after myocardial infarction and randomly assigned their insurance-plan sponsors to full prescription coverage (1,494 plan sponsors with 2,845 patients) or usual prescription coverage (1,486 plan sponsors with 3,010 patients) for the targeted drug classes. Starting at randomization, we followed subjects for up to ten 90-day intervals, and used prescription claims to measure their percent days covered (pdc) within each interval for each drug class. We used random effects models to evaluate the relationship of full coverage, time, and the interaction of time and coverage with adherence.

Results: Mean PDC in the first 90 days after randomization in the full (usual) coverage group was 50.0% (44.9%) for statins, 47.9% (45.2%) for BB, 37.6% (33.9%) for ACE/ARB, and 44.7% (43.5%) for clopidogrel. Adherence declined significantly in an approximately linear fashion over time in each drug class and coverage group, with no significant time by coverage group interaction for any of the drug classes. Average adherence throughout follow-up was 5.0% higher for statins, 3.3% higher for BB, and 4.5% higher for ACE/ARB in the full relative to the usual coverage group (each $p < 0.001$). For the referent drug group, clopidogrel, average adherence was 0.7% higher in the full coverage group ($p = 0.43$).

Conclusions: Full coverage yielded an immediate increase in adherence, an effect that persisted at the same level throughout follow-up. Additional approaches to enhance adherence to therapies with proven benefits require evaluation.

36. Contribution of Lifestyle Factors to Healthy-Adherer Bias in Prevalent Users of Antihypertensive and Lipid-Lowering Drugs

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Background: Adherence to drug therapy may be a surrogate marker for overall healthy behaviors leading to healthy-adherer bias in epidemiologic studies. This might be particularly emphasized in users of preventive drugs, such as lipid-lowering (LL) or antihypertensive (AH) agents. However, individual factors contributing to healthy-adherer effects and their quantitative impacts are not well described.

Objectives: To assess associations between prevalent use of and adherence to preventive medications and healthy lifestyle factors in a population-based sample from the National Health and Nutrition Examination Survey, 1999–2008.

Methods: We identified subjects with uncomplicated hypertension or hyperlipidemia without history of diabetes, ischemic heart disease, heart failure, or cerebrovascular disease. We estimated the magnitude of association between prevalent use of AH or LL medications and demographic and lifestyle factors. Lifestyle factors of interest were predictors of cardiovascular disease or cancer risks, including dietary score, body mass index, exercise, smoking, alcohol consumption, multivitamin use, and self-reported health status.

Results: Among 5,069 patients with hypertension (3,310 users and 1,759 nonusers of AH drugs), users were more likely to be older (mean age, 64 vs. 47 years) and women (58% vs. 49%; all $p < 0.05$). After adjustment for age and sex, prevalent users 65 years of older had significantly less current smoking (odds ratio, 0.6), less binge drinking (0.8), more exercise, lower self-reported poor health (0.75), and less chronic obstructive lung disease (0.7). We observed similar associations among patients with hyperlipidemia with and without LL drugs. The associations were stronger among long-term adherers.

Conclusions: In a large representative US population, prevalent use or adherence to LL or AH drugs was associated with healthier lifestyle factors. The results suggest that healthy user or adherer can be explained, in part, by the healthier lifestyles in prevalent users or adherers in the elderly.

37. Examination of Emergency Inpatient Readmissions within 30 Days from the First Hospitalised COPD Exacerbation in England

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Background: COPD exacerbations requiring inpatient admission have a significant impact on patients' quality of life, mortality risk and resource utilisation. The National Health Service (NHS) is limiting reimbursement for readmissions for the same reason occurring within 30 days of discharge.

Objectives: Provide statistics for emergency COPD admissions and emergency readmission within 30 days in England.

Methods: This was a retrospective analysis using Hospital Episode Statistics (HES) population data from England (© 2010, re-used with permission). Patients with at least one emergency admission (April 2005–March 2010) where COPD was the primary diagnosis (ICD-10 J41–44) on the first consultant episode with an admission were included. This first emergency admission for COPD exacerbation was the index admission. Emergency readmissions within 30 days of discharge were counted and stratified by age and sex. Death in hospital was also tabulated. Data cleaning rules for multiple deaths, overlapping admissions and inconsistent discharge dates were developed. The analysis was performed on an IBM Netezza 1,000–1,006 high performance appliance

Results: There were 244,112 emergency admissions for COPD exacerbations during the observation period, which was 3.6% of all emergency admissions. Of the patients with an emergency admission for a COPD exacerbation, 7.2% died in hospital. Among those discharged alive (N = 225,557), 18% of patients had an emergency readmission for any reason, and 8.4% for COPD exacerbation, within 30 days. The COPD-related readmission frequency increased with increasing age (7.2% 45–59 years, 8.4% 60–74 years, 8.7% 75 year or older); it did not differ by sex. The mean time to the emergency readmission for COPD within 30 days (N = 18,859) was 11.8 days (median, IQR: 10 [4–19]); 10.8% of these patients died during their readmission, the proportion increasing with age.

Conclusions: The burden of emergency COPD exacerbation requiring hospitalisation is substantial: 18% of COPD patients experienced an emergency readmission within 30 days, with almost half attributed to COPD. Nearly one in 10 patients died during admission or within 30 days of discharge.

38. Safety of Long-Acting beta Agonists (LABA) with or without Inhaled Corticosteroids in Asthma

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Background: Whether long-acting beta-agonists (LABAs) are safe when combined with inhaled corticosteroids (ICS) in the management of asthma is uncertain. Based on these concerns the U.S. Food and Drug Administration (FDA) has mandated companies who market these drugs to complete a series of large randomized controlled safety trials.

Objectives: We used administrative health records of the population of the province of British Columbia to assess the risk of hospitalization or death in regular users of ICS + LABA compared with regular users of ICS alone or LABA alone.

Methods: We constructed a cohort of asthma patients between 12 and 45 years old from 1997 to 2007. Within this cohort, we matched patients with asthma-related hospitalization or death to up to 20 control subjects based on age, date of entry into the cohort, and up to six measures of asthma severity. We categorized individuals as regular users, non-regular users, or no-users of ICS, LABA, or ICS + LABA in the 12 months prior to the index date and calculated the risk ratio (RR) between comparison groups.

Results: There were 2,797 cases which were matched to 25,014 controls. Compared to regular use of ICS, regular use of ICS + LABA was not significantly associated with an increased risk of adverse asthma events (RR = 1.03 [95% CI 0.79–1.35]). On the other hand, regular use of LABA alone was associated with a significant increase in risk compared to both regular use of ICS (RR = 2.22 [95% CI 1.43–3.45]) or to ICS + LABA (RR = 2.15 [95% CI 1.32–3.48]). Regular users of LABA had to receive ICS for at least three quarters of a year to have a risk comparable to non-regular LABA users. There were no differences between regular users of ICS + LABA who took their medications in separate inhalers compared to those who received ICS and LABA regularly in single inhalers (RR = 0.89 [95% CI 0.55–1.44]).

Conclusions: Regular use of ICS + LABA does not seem to be associated with an increased risk of asthma-related hospitalization or death. The regularity of ICS use in patients who take LABA seems to be an important factor in the prevention of adverse asthma events.

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39. Inhaled Corticosteroid (ICS) Use in Chronic Obstructive Pulmonary Disease (COPD) and the Risk of Pneumoniaa

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Background: ICS are commonly prescribed to patients with COPD, however, a recent Cochrane systematic review of randomized control trials suggested that ICS had an increased risk of pneumonia.

Objectives: To investigate the risk of pneumonia among newly diagnosed COPD patients using different dose equivalents of ICS in a US medical and pharmacy claims database.

Methods: The Marketscan® Commercial and Medicare Supplemental databases were used. Newly diagnosed COPD patients (no diagnosis of COPD in previous 12 months) with at least two COPD diagnoses on different days and no history of pneumonia/ICS use in the past 12 months were included. Patients with a diagnosis of asthma, cystic fibrosis or lung cancer or <45 years old in the 12-month baseline period or oral corticosteroid use in the 5-year follow-up period were excluded. Daily ICS use for each patient was converted into fluticasone equivalents, classified into low-dose (1–499 μg/daily), medium-dose (500–999 μg/daily) and high-dose (≥1,000 μg/daily), and was constructed as a time-dependent variable. Cox regression modeling was employed to compare the risk of pneumonia onset among ICS non-users vs. low-dose, medium-dose and high-dose ICS users. Models were adjusted for baseline characteristics, including age, gender, region, insurance type, COPD diagnosis year, utilization of COPD medications, comorbidity, hospitalizations and emergency room visits.

Results: Of 135,445 qualified patients were identified; average age 67 (SD 13) years; 51.9% were male. During a mean follow-up of 669 days, 28,750 (21.2%) patients had pneumonia. The hazard ratios for ICS indicated a significant increased risk for pneumonia (hazard ratio [HR] = 1.38, 95% CI 1.27–1.49 for low-dose users; HR = 1.69, 95% CI 1.52–1.88 for medium-dose users; and HR = 2.57, 95% CI 1.98–3.33 for high-dose users).

Conclusions: In this large US medical and pharmacy claims database, the use of ICS in newly diagnosed COPD patients appeared to be associated with an increased risk of pneumonia.

40. Relative Exposure to Inhaled Steroids (Ratio "ICS-to-Total Asthma Therapy"): Concordant Data from Electronic Medical Records (EMRs), Claims Data and Patient-Reported Outcomes (PROs)

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Background: In claims data, computation of "ICS-to-total-asthma-therapy" ratios (R) has shown interest to identify asthmatics more at risk of exacerbations, as a result of insufficient exposure to ICS for their level of disease severity, and hence, poor control. However, ratios have seldom been computed from other data sources.

Objectives: To study the relationship between asthma outcomes and ratios computed in young adults (aged <45 years) from different sources: electronic medical records (EMRs) (Cegedim-Strategic-Data), claims data, and patient-reported outcomes (PROs) obtained from a pharmacy-based survey.

Methods: In all settings, the primary comparison was between non users (R = 0%), inadequate users (0 < R < 50%) and adequate users (R ≥ 50%), as to the following outcomes: asthma-related hospitalizations, new episodes of oral steroids or antibiotics use, and Asthma Control Test (Pharmacy-based study).

Results: In claims data (n = 2,162 mean age = 27 years, 52% females), inadequate users had higher rates of hospitalizations ($p < 0.001$), and oral steroids or antibiotics use than other groups ($p < 0.001$ for both). Oral steroids and antibiotics use were more common ($p < 0.001$ for both) among inadequate users in EMRs (n = 4,587, mean age = 28 years, 54% females). In the pharmacy-based survey (n = 919, mean age = 37 years, 55% females), inadequate users were more likely to be poorly controlled, hospitalized for asthma ($p < 0.001$) and to receive oral steroids ($p < 0.001$) for antibiotics ($p < 0.001$).

Conclusions: Despite differences in study designs and in patient baseline characteristics, conclusions were highly concordant between the three data sources, with evidence of poorer control in inadequate users, notably compared to adequate users. Advantages and limitations of each data source for the interpretation of ratios and assessment of control will be discussed.

41. Impact of Omalizumab Initiation on Emergency-Department Visits, Hospitalizations and Corticosteroid Use in Patients with Uncontrolled Asthma Using High-Dose Inhaled Corticosteroids and Long-Acting Beta$_2$-Agonists

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Background: The goal of asthma pharmacologic therapy is to achieve control, defined as limiting the current impairment and reducing the risk for future deterioration and exacerbations. Omalizumab is a monoclonal antibody indicated for moderate to severe allergic asthma patients with inadequately controlled symptoms.

Objectives: This study evaluated the impact of omalizumab on emergency-department (ED) visits, hospitalizations and corticosteroid use among uncontrolled asthma patients using high-dose inhaled corticosteroids (ICS) prior to initiating omalizumab.

Methods: Health insurance claims from the MarketScan database (2002Q1–2009Q1) were analyzed. Patients with ≥12 months of continuous insurance coverage prior to and after the first omalizumab dispensing, ≥8 weeks of high-dose ICS use, ≥8 weeks of long-acting beta$_2$-agonist (LABA) use, and uncontrolled asthma at baseline were included. A retrospective analysis was conducted to quantify the impact of omalizumab on resource use by comparing ED visits, hospitalizations, and corticosteroid use 1 year before and after omalizumab initiation. A 1-year period was chosen to cover any potential seasonality impacts.

Results: A total of 644 patients (mean age: 49.9 years; female: 59.2%) formed the study population. Omalizumab was associated with a 48.6% reduction in the proportion of patients with ≥1 asthma-related ED visits (pre vs. post-omalizumab period: 21.4% vs. 11.0%, $p < 0.001$) and 40.8% reduction in asthma-related hospitalizations (25.0% vs. 14.8%, respectively, $p < 0.001$). Compared to the pre-omalizumab period, the use of ICS decreased significantly after omalizumab initiation (7.8 vs. 6.5 dispensings, $p < 0.001$; 41.9% of patients had a reduction in ICS use). A similar reduction in oral corticosteroid use was observed (5.0 vs. 3.6 dispensings, $p < 0.001$; 53.3% of patients had a reduction in oral corticosteroid use).

Conclusions: The results of the current study showed that omalizumab treatment initiation was associated with statistically significant reductions in ED visits, hospitalizations and corticosteroid use.

42. Effectiveness of Omalizumab on Asthma Exacerbations Following Its Introduction in a Large Cohort of Patients with Severe Uncontrolled Asthma

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Background: Omalizumab has been shown to decrease the risk of hospitalisation or emergency visits in patients with uncontrolled severe allergic asthma as compared to placebo.

Objectives: This longitudinal study observed the conditions under which omalizumab is prescribed in real-life settings; and assessed whether its use, as an add-on therapy alongside standard treatments, decreases the risk of severe asthmatic exacerbations.

Methods: A cohort of adult patients with uncontrolled severe asthma despite optimal treatment with inhaled and oral corticosteroids and a long-acting beta$_2$-agonist, but no treatment with omalizumab upon entry, was assembled. Risk of hospitalisation and/or emergency room visits for asthma exacerbation was assessed using the Andersen–Gill extension of the Cox model for repeated events controlling for age, gender, smoking history, body mass index, gastro-oesophageal reflux, allergic status, allergic rhinitis, treatment, and hospitalisation or emergency room visits for asthma in the 2 months prior to omalizumab treatment.

Results: Overall, 163 physicians recruited 767 patients, of whom 374 took omalizumab at least once (mean observation period: 20.4 months). Omalizumab use was associated with an adjusted relative risk of hospitalisation and/or emergency room visits for asthma of 0.57 (95% confidence interval: 0.43–0.78). In omalizumab users, the adjusted relative risk of hospitalisation and/or emergency room visits for asthma during omalizumab treatment vs.

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non-treatment periods was 0.40 (95% confidence interval: 0.28–0.58).

Conclusions: Add-on omalizumab significantly decreases the risk of hospitalisation/emergency room visits in patients with uncontrolled severe asthma in the real-life practice.

43. Pattern of Anticoagulation Control and Risk of Stroke, Bleeding and Mortality

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Background: Anticoagulation with warfarin, if well controlled, reduces the risk of ischaemic stroke in patients with atrial fibrillation (AF). There are only limited data on how best to describe the long-term pattern of anticoagulation control, including variations over time.

Objectives: To evaluate and compare different methods for describing International Normalized Ratio (INR) over time in predicting the risk of stroke, bleeding and overall mortality.

Methods: The study cohort consisted of adults aged >40 years with AF and with at least 3 laboratory records of INR within 6 months in the UK General Practice Research Database. Two methods were used to describe INR control; (1) percentage of time spent within therapeutic range (2.0–3.0) and (2) determination of different patterns of INR control using factor and cluster analysis. Nested case-control studies determined the risk of stroke, bleeding and mortality. Furthermore, the additional value of cluster analysis compared to percentage of time in range for prediction of outcomes was determined.

Results: The study population included 27,381 patients with a median follow-up of 3 years. The risks of stroke (<30% HR 2.60 95% CI [1.69–3.98]), major bleed (<40% HR 1.26 95% CI [1.04–1.52]), minor bleed (<40% HR 1.55 95% CI [1.22–1.96]) and mortality (<30% HR 3.76 95% CI [3.0–4.68]), were higher in patients with low percentage of time spent within therapeutic range compared to patients who were in therapeutic range at all times. From a total of six identified clusters, cluster 2 and 6 (both most unstable INR patterns), where associated with an increased risk of mortality (HR 3.37 95% CI [2.71–4.2], HR 10.7 95% CI [8.27–13.85]), major (HR 1.45 95% CI [1.16–1.81], HR 1.6 95% CI [1.13–2.26]) and minor (HR 1.81 95% CI [1.35–2.41], HR 2.13 95% CI [1.39–3.27]) bleed, and stroke (HR 2.14 95% CI [1.4–3.25], HR 3.42 95% CI [2.08–5.63]).

Conclusions: We confirmed that percentage of time in range predicts risk of stroke, bleeding and overall mortality. Cluster analysis of INR patterns improved prediction, beyond percentage of time spent in therapeutic range and may help to identify high risk patients who will need careful monitoring.

44. The Use of Single, Dual, or Triple Antithrombotic Therapy and the Risk of Bleeding Events in Patients with Atrial Fibrillation

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Background: Patients with atrial fibrillation (AF) often receive, in addition to warfarin, antithrombotic agents to manage other comorbid conditions. Few population-based studies have quantified the bleeding risk associated with the concurrent use of these therapies.

Objectives: To quantify the bleeding risk associated with single therapy of warfarin, aspirin, and clopidogrel, as well as combinations of these in patients with AF.

Methods: Using the General Practice Research Database, a nested case-control analysis was conducted within a population-based cohort of patients diagnosed with AF between 1993 and 2008. All cases experiencing a bleeding event during follow-up were matched with up to ten controls on age, sex, and date of cohort entry, selected from the case's risk set. Conditional logistic regression was used to estimate adjusted rate ratios (RR) of bleeding associated with current use of warfarin, aspirin, and clopidogrel in single therapy, as well as in dual and triple therapy, as compared with non-use of any therapy. All RRs were adjusted for potential confounders, which included lifestyle habits (smoking, excessive alcohol use) and comorbidities/drug use.

Results: The cohort included 70,766 patients with AF, of whom 10,850 experienced a bleeding event during follow-up (rate: 4.2/100/year). In single therapy, the use of warfarin was associated with the highest increased risk (RR: 2.07, 95% CI: 1.93–2.22), followed by clopidogrel (RR: 1.63, 95% CI: 1.42–1.88) and aspirin (RR: 1.25, 95% CI: 1.17–1.34). In dual therapy, a higher increased risk was observed for combinations containing warfarin (warfarin-aspirin: RR: 2.87, 95% CI: 2.58–3.18, and warfarin-clopidogrel: RR: 2.79, 95% CI: 2.17–3.57), than those not containing warfarin (aspirin-clopidogrel: RR: 1.71, 95% CI: 1.46–1.99). Triple therapy of warfarin-aspirin-clopidogrel was associated with the highest increased risk (RR: 3.80, 95% CI: 2.74–5.26).

Conclusions: This large population-based study suggests that all antithrombotic therapies are associated with an elevated risk of bleeding, though the risks increase with dual and triple therapy, particularly in combinations containing warfarin.

45. Intrauterine Devices and the Risk of Uterine Perforations: Interim Results from the EURAS-IUD Study

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Background: Uterine perforation is a potentially serious complication of intrauterine device (IUD) use. The absolute risk of uterine perforation associated with levonorgestrel-releasing IUDs (LNG-IUD) is unknown. It is also unknown whether the perforation rate is higher with this IUD than with copper IUDs.

Objectives: Aim of the study is to determine the uterine perforation rate in women using Intrauterine Devices (IUD).

Methods: Large, comparative, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: LNG-IUDs and copper IUDs. The combined cohort will include approximately 60,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden). The study started in 2006 and recruitment will end in 2012. Both the women and their treating physicians receive a follow-up questionnaire 12 months after enrolment. All patient-reported outcomes of interest are validated by the women's treating physicians. A multifaceted four-level follow-up procedure ensures low loss to follow-up rates. The analysis is based on Cox regression models comparing the cohorts.

Results: In October 2011 54,584 women were recruited (70% LNG-IUDs, 30% copper IUDs). The interim results found 31 perforations with LNG IUD (0.81 per 1,000 insertions [95% CI: 0.55–1.15]) and eight with copper IUD (0.49 per 1,000 insertions [95% CI: 0.21–0.97]). Thirty of the 39 perforations were associated with potential risk factors for perforation (e.g., breast feeding, anatomical anomalies). None of the perforations led to generalized septic syndromes, nor to malfunctions of the bowel or bladder. A total of 35 contraceptive failures have been reported (six LNG-IUD, 29 copper-IUD), giving a contraceptive failure rate of 0.02 (95% CI: 0.01–0.05) per 100 women years for LNG-IUD and 0.26 (95% CI: 0.17–0.37) for copper-IUD. The contraceptive failure rate ratio for LNG-IUD vs. copper-IUD was 0.08 (95% CI: 0.03–0.19). Updated results will be presented at the ISPE meeting.

Conclusions: Perforation rates for the two cohorts were within the expected range of 0.5–1.0/1,000 insertions. Review of other safety outcomes did not show a safety signal for LNG-IUD compared to copper IUDs.

46. Selective Serotonin Reuptake Inhibitor Use and Perioperative Bleeding and Mortality in Patients Undergoing Coronary Artery Bypass Grafting

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Background: By reducing platelet serotonin levels, selective serotonin reuptake inhibitors (SSRIs) might reduce platelet aggregation and increase bleeding risk. Several small studies report mixed findings about the safety of SSRI exposure among patients undergoing coronary artery bypass grafting (CABG).

Objectives: To compare in-hospital post-CABG bleeding and mortality rates among patients exposed to SSRIs, other antidepressants (ADs), and no ADs.

Methods: We assembled a cohort of patients who underwent CABG between 2004 and 2008 using the Premier database, which captures inpatient claims data for approximately one in six hospitalizations in the US. In order to measure pre-CABG antidepressant exposure, we included only CABG procedures performed on hospital day ≥2. We classified patients' exposure status according to whether they received SSRIs or other ADs on any hospital day prior to CABG. Patients with no antidepressant exposure prior to CABG formed the referent group. We identified potential confounders at the patient-, surgery-, and hospital-levels. We defined post-CABG bleeding events as transfusions of ≥3 units of packed red blood cells on a single day, any transfusion of platelets, fresh frozen plasma or cryoprecipitate, or any upper or lower gastrointestinal endoscopy. We used adjusted Cox proportional hazards models to compare bleeding and mortality rates among the three exposure groups. In sensitivity analyses, we further stratified the Cox models on hospital day of CABG.

Results: Of 132,680 eligible patients, 7,112 received pre-CABG SSRIs, 1,905 received other ADs, and 123,663 received no ADs. The incidence of major bleed was 4.0% and 3,643 (2.7%) patients died. Compared to no exposure, neither SSRIs (HR, 0.94; 95% CI, 0.83, 1.06) nor other ADs (1.03; 0.82, 1.29) increased major bleeding risk. Neither SSRIs (0.94; 0.82, 1.09) nor other ADs (0.83; 0.62, 1.12) increased mortality risk. Stratification by day of CABG did not alter the results.

Conclusions: In this study of >100,000 patients undergoing CABG, we did not observe an increased risk of bleed or death associated with pre-operative SSRI or other AD exposure.

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47. Risk of Acute Myocardial Infarction (AMI), Stroke, and Death in Parkinson's Disease (PD) Patients Treated with Entacapone (Entac) or Other Adjunctive Therapies (AT)

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Background: Entac is a COMT inhibitor that modestly reduces on-off fluctuations in PD patients treated with L-dopa. The randomized trial, STRIDE-PD, unexpectedly found an increased risk of AMI with Entac vs. placebo in PD patients.

Objectives: To test if AMI, stroke, or mortality risk is increased in PD patients treated with Entac compared with other AT.

Methods: Propensity score (PS)-matched retrospective new-user cohorts of patients initiating Entac or AT (dopamine agonists and/or selective MAO-B inhibitors) from 2007 to 2010. PS model included variables for socio-demographics, cardiovascular disease (diagnoses, drugs), other chronic medical conditions (diagnoses, drugs), L-dopa treatment history, PD-related complications, and frailty indicators.

Setting: Community-dwelling, Medicare beneficiaries age ≥65 years with at least 12 months prior enrollment in Parts A, B, and D, ≥2 prior PD diagnoses, and prior L-dopa treatment.

Exposures: Entac vs. AT (reference).

Outcomes: Hospitalized AMI, stroke, and death while on therapy. Pre-specified analyses for effect modification by treated diabetes, ischemic heart disease, kidney failure, and complications of PD were performed.

Statistics: Cox proportional hazards regression.

Results: Cohorts included 8,681 Entac- and 17,362 AT-treated PD patients with close covariate balance, contributing 7,954 person-years of follow-up on treatment, during which there were 106 AMIs, 89 strokes, and 201 deaths. The adjusted hazard ratios (HR) (95% CI) comparing Entac with other AT were 0.86 (0.57–1.30) for AMI, 0.85 (0.54–1.35) for stroke, and 0.79 (0.58–1.07) for death. There was effect modification of stroke risk by PD complications status: PD without complications – HR (stroke) = 0.48 (0.26–0.89); PD with complications – HR (stroke) = 2.18 (1.02–4.63).

Conclusions: The risks of AMI, stroke, and death were not increased in PD patients treated with Entac compared with AT. Risk of stroke was reduced in Entac-treated patients without complicated PD and increased in Entac-treated patients with PD complications. Additional study of this unexpected effect is needed.

48. Heralding of STEMI and NSTEMI: A Prospective CALIBER Study

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Background: Large, prospective evaluations of atherosclerotic disease manifestations and risk factors among people who eventually experience ST-elevation myocardial infarction (STEMI) and non ST-elevation myocardial infarction (NSTEMI) have not previously been reported.

Objectives: To compare the evolution of atherosclerotic disease and cardiovascular risk between people with STEMI and NSTEMI.

Methods: We linked electronic health records in primary care from the UK GPRD (median 9 years' prospective data on the onset and prevalence of coronary, cerebrovascular and peripheral arterial disease, risk factors and use of blood pressure lowering, lipid lowering and antiplatelet medications) to the national registry of myocardial infarction, (the Myocardial Ischaemia National Audit Project) and compared patients with STEMI (n = 3,780) and NSTEMI (n = 4,394).

Results: Overall 29% (95% CI 28–31%) of STEMI patients and 51% (49–52%) of NSTEMI patients were heralded by previous atherosclerotic disease. Patients with NSTEMI were more likely to have atherosclerotic disease at more than one arterial site (NSTEMI 15% ≥2 sites, STEMI 6%) and longer-standing disease. The majority of prior atherosclerotic disease was coronary but a third of heralding in STEMI and a fifth in NSTEMI was peripheral or cerebrovascular alone. There was a 3 month period preceding both STEMI and NSTEMI during which the rate of coronary disease diagnoses was increased, but there was no equivalent increase in the rate of peripheral or cerebral diagnoses. In patients without any diagnosed atherosclerotic disease, 79% of STEMI and 80% of NSTEMI patients had at least one elevated risk factor, but prevalence of all risk factors, except smoking, was higher in patients with NSTEMI.

Conclusions: The longitudinal pattern of prior atherosclerotic disease and risk factors is markedly different for STEMI and NSTEMI, supporting the hypothesis that STEMI and NSTEMI are two different pathophysiological entities. The high prevalence of heralding and the long duration between first diagnosis and MI implies that for many patients there is ample opportunity to provide appropriate secondary prevention.

49. Risk of Bladder Cancer in Diabetic Patients Treated with Rosiglitazone or Pioglitazone: A Nested Case-Control Study

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Background: Evidence has emerged that pioglitazone may increase the risk of bladder cancer, but the association has not been confirmed. This potential risk also has not been evaluated in users of rosiglitazone.

Objectives: Using Taiwan's National Health Insurance research database (NHIRD), this large population-based nested case-control study was conducted to explore the relationship between the use of thiazolidinediones (rosiglitazone and pioglitazone) and risk of bladder cancer in diabetic patients.

Methods: We identified 3,412 cases of newly diagnosed bladder cancer and 17,060 controls among diabetic patients. Multivariable conditional logistic regressions were used to estimate the association between exposure (timing and duration) to thiazolidinediones and bladder cancer. Duration of rosiglitazone or pioglitazone use was defined based on the cumulative days of exposure prior to the index date : <1, 1–2, and >2 years.

Results: Rosiglitazone and pioglitazone use were associated with risk of bladder cancer and the associations were stronger with longer term of exposure to thiazolidinediones (pioglitazone $<$ 1 year odds ratio (OR) 1.45 (95% confidence interval (CI) 1.12–1.87, $p < 0.01$), 1–2 years OR 1.74 (95% CI 1.05–2.90, $p = 0.03$), and ≥2 years OR 2.93 (95% CI 1.59–5.38, $p < 0.01$); rosiglitazone $<$ 1 year OR 0.98 (95% CI 0.82–1.17, $p = 0.81$), 1–2 years OR 1.78 (95% CI 1.31–2.39, $p < 0.01$) and ≥2 years OR 2.00 (95% CI 1.37–2.92, $p < 0.01$).

Conclusions: Long-term exposure to thiazolidinediones (pioglitazone and rosiglitazone) was associated with higher odds of bladder cancer, and the highest odds were seen in thiazolidinedione users with ≥2 years of exposure.

50. Long-Term Therapy with Thiazolidinediones May Be Associated with Increased Incidence of Bladder Cancer

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Background: Several regulatory agencies recently warned prescribers that use of pioglitazone (PIO), a thiazolidinedione (TZD), may increase the risk of bladder cancer. France and Germany removed the drug from their markets, although the rest of Europe did not. The risk from other TZDs is unknown.

Objectives: To compare bladder cancer risk with use of TZDs relative to sulfonylureas (SUs), and between PIO and rosiglitazone (ROSI).

Methods: This cohort study included 59,855 patients with type II diabetes mellitus who initiated treatment with a TZD or sulfonylurea (SU) from 2000 to 2010 using The Health Improvement Network database. Exposure to a TZD was defined as receipt of two prescriptions for either ROSI or PIO within 6 months. The primary outcome was an incident diagnosis with bladder cancer. We used Cox proportional hazards models to calculate relative hazards of bladder cancer in patients exposed to TZDs in comparison to the reference group of SU users, adjusted for confounders. Cox regression was also used to assess whether the relative risk of bladder cancer increased with increasing duration of TZD therapy and time since initiating a TZD.

Results: There were 60 incident diagnoses of bladder cancer in the TZD cohort ($n = 18{,}459$) and 137 in the SU cohort ($n = 41{,}396$). There was no significant difference in bladder cancer risk between the cohorts (HR 0.93, 95% CI 0.68–1.29) when short term exposure was included in the exposure definition. In contrast, the risk of bladder cancer was increased among patients with the longest duration of TZD vs. SU therapy (HR 3.25 [95% CI 1.08–9.71] for ≥5 years of use), and among those with the longest time since initiation of therapy (HR 2.53 [95% CI 1.12–5.77] for ≥5 years since first use). Bladder cancer risk also increased with increasing time since initiation of pioglitazone (p-trend < 0.001) and rosiglitazone (p-trend $= 0.006$). Direct comparison of pioglitazone to rosiglitazone did not demonstrate significant differences in cancer risk ($p = 0.49$) or with increasing time since initiation (p-trend $= 0.12$) or duration of therapy (p-trend $= 0.75$).

Conclusions: Long-term TZD therapy may be associated with an increased risk of bladder cancer, which appears to be a class effect.

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51. Effect of Metformin vs. Other Antidiabetic Drugs on Colorectal Cancer Stage

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Background: Preclinical and observational studies suggest that use of metformin, a non insulin-releasing antidiabetic drug (ADD), reduces cancer risk. Laboratory studies suggest metformin prevents tumour metastases. We investigated, for the first time, associations between metformin use and tumour stage at diagnosis in colorectal cancer (CRC).

Objectives: To determine associations between metformin exposure (vs. other ADDs) and likelihood of presenting with no nodal or metastatic tumour involvement (node-met-) in CRC.

Methods: National Cancer Registry Ireland records were linked to state-funded (means-tested) prescription claims data and used to identify incident stage TI-TIII CRC diagnosed 2001–2006 in this cohort study. Patients who received ADDs in the year prior to diagnosis were divided into three groups; those who received metformin only (MET), those who received ADDs other than metformin (OTHER) and those who received both (BOTH). The metformin-receiving groups were subdivided into high/low metformin exposure. Multivariate logistic regression models were used to predict the probability of node-met-status for each drug exposure group. Odds ratios (OR) were adjusted for age, sex, tumour size and grade, comorbidity, year of diagnosis, smoking and aspirin exposure. Adjusted risk differences were estimated using log-binomial regression to aid interpretation.

Results: Of 3,588 stage TI–TIII CRC patients were identified; 294 patients received an ADD in the year prior to diagnosis. Exposures were as follows: MET (high): n = 43, (low): n = 34; BOTH (high metformin): n = 49, (low metformin): n = 67; OTHER: n = 101. MET (high exposure), relative to OTHER, was associated with a significantly increased likelihood of node-met- diagnosis (OR = 2.59, 95% CI 1.16–5.76). This corresponded to a log-binomial estimated risk difference of 0.20 (95% CI 0.02–0.38). This benefit was limited to patients who received metformin without any other ADDs.

Conclusions: High exposure to metformin (relative to other ADDs) was associated with less advanced CRC at diagnosis. This benefit was not observed in patients with high metformin exposure who also received other ADDs. These results affirm preclinical findings.

52. Comparative Lung Cancer Mortality with Inhaled Insulin or Comparator: An Observational Follow-Up Study of Patients Previously Enrolled in Exubera Controlled Clinical Trials (FUSE)

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Background: Exubera was the first inhaled insulin approved for treatment of diabetes mellitus. An imbalance of newly diagnosed lung cancer cases was observed in the Exubera clinical program but may have been due to case ascertainment/diagnostic bias. Follow-up of the Exubera clinical program population provided the largest source population for study of Exubera use and lung cancer risk.

Objectives: To estimate the primary lung cancer mortality rates and corresponding rate ratio among Exubera- (EXU) and comparator-treated (COMP) subjects.

Methods: A non-interventional follow-up study of primary lung cancer among subjects previously enrolled in any of 17 prior Exubera clinical studies, with retrospective and prospective components. Sites from 25 countries participated in FUSE and enrolled patients were followed for an additional 2 years for incidence of fatal primary lung cancer, all-cause mortality and primary lung cancer incidence.

Results: (Preliminary, final adjudicated results available April 2012) Of 7,448 patients in the original trials (all contributed retrospective data), 4,356 were from sites that participated in FUSE and were eligible to participate in the prospective follow-up. Of these, 2,637 (60.5%) were enrolled, 10% more than anticipated. Comparing total person-years (PYs) (retrospective + prospective) there were 12,327 PYs among EXU and 11,614 PYs among COMP. Reports of primary lung cancers were higher in EXU (14) compared with COMP (4) (crude hazard ratio (HRc) = 3.23; 95% CI 1.06–9.80). The incidence rate of reported primary lung cancer mortality was 0.45 per 1,000 PYs for EXU and 0.19 per 1,000 PYs for COMP, (HRc = 2.30; 95% CI 0.45–11.85). The incidence rate of all-cause mortality was 6.70 per 1,000 PYs for EXU and 8.43 per 1,000 PYs for COMP (HRc = 0.79; 95% CI 0.58–1.07).

Conclusions: Based on un-adjudicated reports, there appears to be a 3.2-fold risk of lung cancer and 2.3-fold risk of lung cancer mortality among patients randomized to Exubera. There was no evidence of increased risk of all cause mortality.

53. Risk of First Severe Hypoglycaemic (SH) Coma Event among Patients with Diabetes Who Initiate the Use of Detemir (IDet), Glargine (IGla) and NPH Insulins: A Nationwide Register-Linkage Study in Finland

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Background: Long-acting basal insulin analogues have been shown to have a positive effect on the balance between effective glycaemic control and hypoglycaemic risk compared to NPH insulin in randomized studies. Evidence from real-life use settings is needed.

Objectives: To estimate and compare the incidence of SH coma events, among diabetes patients who initiate the use of detemir, glargine, and NPH insulins.

Methods: This is a nationwide register-linkage cohort study of the Finnish health care databases during the follow-up period 2000–2009. The study cohort contained all insulin naive diabetic patients and who had purchased at least one prescription of insulins during the follow-up period 2000–2009. Prescriptions were converted into continuous drug exposure periods based on the defined daily doses purchased. SH coma event which was defined as an event leading to hospitalization or a visit to secondary health care due to hypoglycaemic coma. The adjusted hazard ratio (HR) estimates with 95% confidence intervals (CI) were estimated using the conventional Cox proportional hazards model. The robustness was evaluated in sensitivity analyses.

Results: Total population comprised 137,994 patients and 75,682 (54.8%) of them were insulin naive. Five thousand six hundred and sixty-nine patients experienced at least one SH event during a mean follow-up time of 3.9 years. The crude incidence (per 1,000 years) of first SH event was 13.52 (IDet), 18.25 (IGla) and 20.78 (NPH). HR (95% CI, p-value) were 0.74 (0.64–0.85, <0.001) for Idet and 0.88 (0.81–0.97, 0.006) for Igla when NPH was used as reference. Idet had a 16.6% (5.1–26.7%, 0.006) lower SH risk than Igla. Sensitivity analyses suggested statistically significant risk reductions with HR varying between 0.71 and 0.86 for Idet vs. NPH and between 0.85 and 0.90 for Igla vs. NPH. This translates into a 2.2–19.6% lower SH risk for Idet when compared to Igla.

Conclusions: Our real-life data shows a robust lower risk of SH for IDet and IGla when compared to NPH. The risk of hospitalisation due to SH could potentially be modified by the selection of the long-acting insulin.

54. Characteristics of Patients Initiating Oral Antidiabetic Therapy in the UK: Evidence of Delayed Treatment?

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Background: Type 2 diabetes (T2D) represents 85% of all diabetes. If life style counselling is ineffective at controlling hyperglycemia (A1c > 48 mmol/mol) oral antidiabetic therapy (OAD), usually metformin, is indicated. With the introduction of the UK's Quality Outcomes Framework (2004) incentivising systematic recording of measures such as A1c and the increased level of computerised lab linkage, it is now possible to evaluate treatment with respect to this marker of effectiveness.

Objectives: To describe the current patterns of OAD administration including A1c distribution, BMI, time since onset of diabetes, demographics and comorbidities.

Methods: This cohort study takes baseline data from 63,060 patients initiating OAD identified in the General Practice Research Database between 1/1/2006 and 1/2/2011 and is representative of diabetes care in the UK.

Results: Median age at initiation of OAD was 62 years (57% male). Approximately 70% of patients were diagnosed (dx) prior to OAD initiation. The median time from first dx code to OAD initiation was 11.6 months (range < 1–515.9 months). The majority (74.4%) of patients had a record of A1c prior to OAD initiation the median value being 65 mmol/mol (IQR 57–80); 25% had a value in excess of 80 mmol/mol. Overall, over half the patients were obese (median BMI = 31.2 mg/k^2), prevalence of heart disease was 17% and the most frequent microvascular complication was retinopathy (4.5%). Most patients initiated treatment with metformin as monotherapy (88%), gliclazide (8.1%), metformin with gliclazide (1.5%). Median A1c levels were lower in patients dx prior to OAD initiation (64 vs. 75 mmol/mol) with a quarter having levels >77 mmol/mol. Patients dx with T2D prior to OAD were older (63 vs. 59 years) and had higher prevalence of heart disease (19% vs. 13%).

Conclusions: This study confirms the high use of metformin as first line OAD per UK guidelines, however many patients initiate OAD with HbA_{1c} values far in excess of the recommended levels. For approximately 30% of these patients, the diagnosis of T2D coincided with OAD.

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55. Time Trends in Antihypertensive Drug Use and Blood Pressures in Swedish Primary Health Care 2001–2008

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Background: The efficacy of antihypertensive drug therapy is undisputed, but observational studies show that few patients reach target blood pressures < 140/90 mmHg. However, there is limited data on time trends in utilization and effectiveness of drug therapy in real practice.

Objectives: This study aimed at describing long-term trends in blood pressure levels and antihypertensive drug treatment in a Swedish primary health care population with diagnosed hypertension.

Methods: In this retrospective cross-sectional study, data was extracted from electronic patient records in 48 primary healthcare centers in two Swedish regions. All patients ≥30 years with a recorded diagnosis of hypertension who consulted the general practitioners between 2001 and 2008 were included (n = 75,219). Clinical data on diagnoses and blood pressures were linked to data on dispensed drugs to monitor drug utilization over time. Main outcome measures were mean systolic and diastolic blood pressures, and the proportion of patients purchasing different antihypertensive drugs.

Results: The proportion of patients reaching target blood pressure increased by twenty percent from 14% in 2001 – to 34% in 2008 and mean systolic blood pressure decreased 10 mmHg during the same period. The patients purchasing angiotensin converting enzyme inhibitors, angiotensin receptor blockers and calcium channel blockers increased from 26%, 19% and 29% in 2005 to 42%, 24% and 35% in 2008, respectively. During the same period there was an increase in the number of antihypertensive drugs per patient.

Conclusions: There is a positive trend in the proportion of patients with diagnosed hypertension that reaches target blood pressure. Part of the explanation may be the increasing number of patients purchasing antihypertensive drugs.

56. Predictors of First-Step Antihypertensive Treatment among Older Adults at High Risk for Cardiovascular Outcomes

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Background: Controversy continues regarding initial choice of treatment for hypertension in older and very old patients with at least one more risk factor for cardiovascular diseases (CVD). It is unknown how prescribing patterns in clinical practice differ from guideline recommendations for thiazides (THZ) in this population.

Objectives: To describe characteristics of new users of antihypertensive medication and identify predictors of initial choice of treatment in an older population (≥65 years) at elevated risk for CVD.

Methods: We conducted a retrospective cohort study using Medicare claims (Parts A, B, and D) from 2006 to 2009. Our cohort included new users of antihypertensives, ≥65 years, at elevated risk for CVD and continuously enrolled 1 year prior to initiation. Antihypertensives included THZ, calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin II receptor blockers (ARB). We used multivariable logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between baseline characteristics (gender, age, race, comorbidities) and treatment with an ACEI, ARB or CCB compared to THZ.

Results: Of 142,973 new users, 61.1% were female and 84.4% were White. At baseline 30.4% (N = 43,397) had type 2 diabetes and 82.5% (N = 117,864) had hyperlipidemia. Among new users, 48.7% (N = 69,510) initiated an ACEI; 24.8% (N = 35,454) a CCB; 13.8% (N = 19,714) a THZ; and 12.7% (N = 18,115) an ARB. Males were more likely to initiate an ACEI (OR = 1.6, CI: 1.5, 1.6); African-Americans were more likely to initiate a CCB than Whites (OR = 1.4, CI: 1.3, 1.5). Those with type 2 diabetes were more likely to initiate an ACEI (OR = 2.5, CI: 2.4, 2.6) or ARB (OR = 2.0, CI: 1.9, 2.1).

Conclusions: This study highlights differences in hypertension treatment among Medicare beneficiaries 65 and older. Despite results of a head-to-head randomized trial showing that THZs were as effective as other antihypertensives, only a minority of patients are started on THZs. In clinical practice, gender and race (in additional to comorbid conditions) appear to influence the choice of initial treatment.

57. Oral Hypoglycemic Agent Adherence and Hospitalization among Patients with Type 2 Diabetes: A Call for Enhanced Guidelines

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Background: Medication adherence has been identified as an important factor influencing health outcomes for patients with type 2 diabetes (DM2). The clinical impact of poor adherence, however, in patients with DM2 is poorly characterized.

Objectives: To assess adherence to oral hypoglycemic agents (OHA) and its relation to hospitalizations in DM2 diabetes patients enrolled in Wellpoint and Medicaid insurance.

Methods: A longitudinal retrospective study of patients with DM2 with OHA dispensing data between 2002 and 2008 in our health information exchange (HIE), the Indiana Network of Patient Care (INPC). OHA adherence was measured by the proportion of days covered (PDC) in every 6-month interval starting from the patient's first OHA dispensing event. Odds ratios (OR) were used to quantify the magnitude of associations between OHA adherence and hospitalizations. The analysis controlled for patient demographic and clinical factors.

Results: Among 25,175 eligible patients, 9,472 were Medicaid beneficiaries (68% female, 77% white and mean age of DM2 onset 45 years) and 13,125 were Wellpoint beneficiaries (51% female, 87% white and mean age of DM2 onset 50 years). The average 6-month PDC was 0.47 and 0.54 for Medicaid and Wellpoint patients, respectively. Using a conventional 80% cutoff point, the percentage of nonadherent patient was 93% and 90% for Medicaid and Wellpoint respectively. The proportion of patients who had at least one hospitalization was 35% for Medicaid, and 28% for Wellpoint. In the adjusted analysis, nonadherent patients had a significantly higher risk of hospitalization in both groups (OR: 1.55, 95% CI: 1.40–1.70; $p < 0.0001$ for Medicaid and OR: 1.23, 95% CI: 1.15–1.35; $p < 0.0001$ for Wellpoint). Other factors that slightly affected hospitalization were age of DM2 onset (0.99, $p < 0.0001$), African-American ethnicity (0.87, $p < 0.0001$), and Hispanic ethnicity (0.73, $p < 0.0001$). Gender and number of concurrent OHA had no significant effect on hospitalization.

Conclusions: Longitudinal, clinical data from an operational HIE confirmed that OHA adherence is suboptimal for patients with type 2 diabetes in both Medicaid and Wellpoint populations.

58. Drug Treatment after Transient ischaemic Attack or Ischaemic Stroke: Are We Doing Enough to Reduce Secondary Risk?

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Background: Australian stroke management guidelines (published in 2007) recommend prescribing of antithrombotic, antihypertensive and lipid lowering medicines for all transient ischaemic attack (TIA) and ischaemic stroke (IS) patients to reduce secondary risk.

Objectives: To investigate use of guideline-recommended medicines after hospitalisation for TIA or IS.

Methods: A drug utilisation study was conducted using health administrative claims data from the Australian Government Department of Veterans' Affairs. Data was extracted for veterans discharged from hospital between 1/1/2009 and 31/12/2009 with a primary diagnosis of TIA or IS. Only the first discharge during the study period was included for analysis. Dispensing of antithrombotics, antihypertensives and lipid lowering medicines within the 120 days before and after hospitalisation was determined. Kaplan Meier analyses were undertaken to identify the proportion of subjects dispensed each medicine and the combination of all three recommended medicines after hospitalisation.

Results: Of the 2,360 subjects (1,190 TIA, 1,170 IS) included, mean age was 85 years, 49% were male, with multiple comorbidities (mean Rx-risk = 4). A total of 2,127 subjects (1,177 TIA, 950 IS) were discharged alive after hospitalisation. Prior to hospital admission, utilisation of antihypertensives was high (77% TIA, 78% IS), with moderate use of antithrombotics (62% TIA, 54% IS) and lipid lowering medicines (47% TIA, 41% IS). After hospitalisation, the proportion of veterans dispensed antithrombotics (85% TIA, 89% IS), antihypertensives (82% TIA, 85% IS) and lipid lowering medicines (60% TIA, 71% IS) increased. Forty-eight percent of TIA subjects and 59% of IS subjects were dispensed the combination of all three recommended medicines after hospitalisation.

Conclusions: Increased use of antithrombotics, antihypertensives and lipid lowering medicines is consistent with stroke guideline recommendations. Further research is necessary to understand what factors, such as age or comorbidities, are influencing potentially sub-optimal medicines use within this population.

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59. Potentially Inappropriate Drugs in Elderly Hypertensive Patients with Impaired Renal Function

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Background: Adverse drug reactions in elderly are often consequences of potentially inappropriate drugs (PID) with regard to renal function. PID refers to contraindicated drugs or drugs that have to be avoided or monitored in patients with impaired renal function.

Objectives: To quantify the utilization of PID in elderly hypertensive patients with estimated glomerular filtration rate (eGFR) < 60 mL/min.

Methods: Design: Cross-sectional study based on the Swedish primary care cardiovascular database (SPCCD), covering all patients with hypertension (78,000) in 48 primary care centres and including laboratory data, diagnoses, and dispensed drugs. All substances dispensed repeatedly (≥3 prescriptions dispensed/year) to ≥2% of the population were analysed for 2007–2008. eGFR was calculated with Cockcroft-Gault-formula.

Setting: Swedish primary care population with hypertension, median age 74 (interquartile range (IQR) 69–80), from rural and urban areas, with data on creatinine, weight and length, n = 10,684. The proportions for comorbidities were (%): transitory ischemic attack (2.3), cerebrovascular disease (9.8), diabetes type 2 (45.3), atrial fibrillation (9.8), cardiac insufficiency (9.4), ischemic heart disease (20.2).

Main outcome measure: Proportion of patients with eGFR 30–59 mL/min (chronic kidney disease (CKD) stage 3) or eGFR < 30 mL/min (CKD stage 4/5) who were dispensed PID.
Statistical analysis: Continuous data: mean (SD) or median (IQR).

Results: Mean eGFR was 74.5 mL/min (SD 26.6). A total of 27 substances were dispensed to patients having CKD stage 3 (n = 3,089, 28.9%). Nearly half of the substances (n = 13) were potentially inappropriate, the most common being enalapril (dispensed to 16.7% of patients), atenolol (13.1%) and metformin (8.4%). A total of 24 substances were dispensed to patients having CKD stage 4/5 (n = 256/2.4%). Halv of the substances (n = 12) were potentially inappropriate, the most common being enalapril (dispensed to 11.3% of patients), atenolol (9.8%) and candesartan (7.4%).

Conclusions: Elderly hypertensive patients with CKD stage 3–5 receive a substantial amount of drugs contraindicated in impaired renal function or requiring monitoring and follow-up.

60. Prevalence of Potentially Inappropriate Medication Prescribing among Older US Adults

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Background: Potentially inappropriate medications (PIM) increase the risk of adverse effects of drugs in older adults. Beers Criteria have been used internationally to identify PIM but recent US data are lacking.

Objectives: To determine prevalence rate of PIM among US elderly population.

Methods: We used fee-for-service Medicare Parts A, B, and D claims data from 2007 to 2009 to estimate the prevalence of PIM in the US population aged ≥65 years. PIM was defined by Beers 2003 Criteria, including diagnoses or conditions present in the previous calendar year. We estimated the point prevalence of PIM within each calendar month by dividing the number of older adults with ≥1 PIM during the month by the number of adults filling ≥1 prescription. The numerator for the period prevalence was the number of older adults with ≥1 PIM during the calendar year. We report the prevalence and used generalized estimating equations (GEE) to account for the dependence of multiple monthly observations of a single person in the estimated 95% confidence intervals (CI).

Results: We report preliminary results for a 0.2% random sample of the study population. A total of 22,875, 24,118 and 25,270 patients were included during 2007, 2008 and 2009, respectively. The mean age was 77.4 ± 7.8 years, 65.4% were women, and 84.4% were white. The point prevalence of PIM was 14.9% (CI: 14.5–15.4) in 2007, 14.5% (CI: 14.1–14.9) in 2008, and 14.4% (CI: 14.0–14.8) in 2009. In contrast, the period prevalence was 29.2%, 29.1%, and 29.5% in 2007, 2008, and 2009, respectively. African Americans (19.1%) and those ≥85 years (16.5%) had higher point prevalence. The most common high severity PIMs were long-term benzodiazepine or sympatholytic agents in patients with depression (1.7%) and anticholinergic drugs, stimulants, and barbiturates in patients with cognitive impairment (1.2%).

Conclusions: Estimating the prevalence of PIM based on any dispensing within a prolonged period (e.g., calendar year) may overestimate the point prevalence by 100%. Psychotropic products were found to have the highest potential for inappropriate prescribing. We are currently comparing Beers with the newer STOPP and START criteria to estimate PIM point prevalence.

61. Treatment of Depression during Pregnancy and Its Effect on Infant NICU Admission

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Background: Depression during pregnancy has been associated with the risk of preterm delivery (PTD) and low birthweight (LBW), a main reason for NICU (Neonatal Intensive Care Unit) admission, a major cause of medical expenditure. Currently, significant confusion exists regarding whether prenatal depression should be treated and, if so, which treatment is most beneficial.

Objectives: To examine the comparative effectiveness of treatment options (antidepressants only, psychotherapy only, or combination of both therapies) on the risk of infant NICU admission.

Methods: We conducted a retrospective cohort study among 445,807 pairs of pregnant women and their live-born infants at Kaiser Permanente, Northern California (KPNC) from 1997 to 2009. Depression diagnosis and treatment in pregnancy and infant NICU admission (>48 hours) were identified through KPNC clinical and pharmacy data. Among women with clinically diagnosed depression in pregnancy, 7.3% received antidepressant treatment only, 41.2% received psychotherapy only and 29.3% received combination therapy.

Results: After controlling for confounders using logistic regression, compared to receiving no treatment, treating prenatal depression by (1) antidepressant medication alone, (2) psychotherapy alone or (3) combination therapy was associated with 15–20% reduction in infant NICU admission: adjusted odds ratio (aOR) = 0.85, 95% confidence interval (CI): 0.77–0.95, aOR = 0.80 (0.73–0.89) and aOR = 0.82 (0.74–0.91), respectively. The benefit of treating depression in pregnancy was further enhanced when we restricted to NICU admissions due to PTD or LBW: aOR = 0.8 (0.69–0.91) for antidepressant medication, aOR = 0.64 (0.56–0.74) for psychotherapy only and aOR = 0.58 (0.51–0.67) for combination therapy, respectively. There was also a dose-response relationship with duration of use.

Conclusions: Our study provides new evidence that treatment of depression with either antidepressant medication or psychotherapy during pregnancy reduces the risk of infant NICU admission, especially when complicated with PTD or LBW.

62. Bipolar Disorder, Mood Stabilizers and Adverse Pregnancy Outcome – A Population Based Cohort Study

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Background: Knowledge concerning treatment with mood stabilizers in pregnant women with bipolar disorder is limited.

Objectives: To study risks of adverse outcomes for treated and untreated bipolar mothers and their infants.

Methods: This is a population based cohort study. Data were retrieved from Swedish national health registers. All women with at least two recorded bipolar diagnoses giving birth in Sweden between 2005 and 2009 were identified. Drug use was determined through prescription fills. The women were grouped by use of mood stabilizing drugs during pregnancy (lithium, antipsychotics and anticonvulsants [n = 320]), or no use of these drugs (n = 554), and were compared to all other women who gave birth (n = 332,137). Outcome measures were congenital malformations, preterm birth, caesarian delivery, gestational diabetes, being born small for gestational age (SGA) or large for gestational age (LGA), and neonatal morbidity. Odds ratios (ORs) were calculated in multivariate logistic regressions, adjusting for potential confounders: maternal age, country of origin, cohabitation, smoking, and height as well as the infants' birth order.

Results: Bipolar mothers were more often smokers, overweight and abused alcohol and drugs. Moreover, they had increased risks of not having a spontaneous start of the delivery (ORs 1.64–2.24, 95% confidence intervals [CIs] 1.35–2.81), and a 50% increased risk of preterm birth. In contrast to the treated mothers the untreated had increased risks of giving birth to infants born symmetrically SGA for both weight and length (OR 2.24, 95% CI 1.20–4.19) and for microcephaly (OR 1.86, 95% CI 1.21–2.86) and neonatal hypoglycemia (OR 1.63, 95% CI 1.07–2.48).

Conclusions: Women with bipolar disorders had increased risks of adverse birth outcomes. Refraining from medical treatment seems to be associated with growth restriction.

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63. Childhood Overweight Following Fetal Exposure to Selective Serotonin Reuptake Inhibitors and Maternal Psychiatric Illness

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Background: In animals, fetal SSRI exposure alters serotonergic regulation of food intake and body weight in later life, influencing risk of overweight.

Objectives: To investigate the association between fetal SSRI exposure and childhood overweight at 7-years of age.

Methods: We used data on 35,910 women enrolled in the Danish National Birth Cohort between 1996 and 2002 who delivered live singletons and completed all four telephone interviews and a self-administered questionnaire when their child was 7-years of age. Pregnancy exposures and prevalence of childhood overweight was based on maternal self-reported data. Of eligible pregnant women, 123 used a SSRI, 467 reported a psychiatric illness but no psychotropic medication use and 35,320 reported no psychiatric illness and no use of psychotropic medication. Childhood overweight was classified as a BMI >85th percentile, based on age and sex. Rates of overweight were compared using a generalised linear model, yielding prevalence ratios (PRs) and 95% confidence intervals (CIs).

Results: In comparison to offspring of women with an untreated psychiatric illness during pregnancy, no statistically significant associations were observed between prenatal SSRI exposure and risk of childhood overweight in male (aPR 1.64; 95% CI 0.92–2.94) or female (aPR 0.30; 0.08–1.11) offspring. However, for female offspring exposed to untreated maternal psychiatric illness during pregnancy we found a smaller, but statistically significant increased risk of overweight at 7-years of age (aPR 1.54; 1.12–2.15) compared with unexposed children. The association was not found for males (aPR 1.02; 0.71–1.46), which may suggest a sex-specific effect.

Conclusions: We did not find a statistically significant association between prenatal SSRI exposure and childhood overweight at 7-years of age. However, we found evidence suggesting outcomes may be sex-specific with female, but not male, offspring exposed to untreated maternal psychiatric illness during pregnancy at increased risk of overweight at 7-years of age. Limitations of this study, including the small number of children exposed to SSRIs, suggest further research may be warranted.

64. Antidepressant Use during Pregnancy and the Risk of Delay in oOverall Cognitive Development at 1 Year Old: Results from the OTIS Antidepressants Study

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Background: Serotonin plays a major role in brain development in utero. It is hypothesized that antidepressants could interact with serotonin level needed during brain maturation.

Objectives: To quantify the risk of delay in cognitive development associated with the use of antidepressants during pregnancy

Methods: To be included in the OTIS Antidepressants Study, women had to (1) call a North American participating teratogen information service during 2006–2010, (2) be ≥18 years old, (3) ≤14 weeks of pregnancy, (4) be exposed to an antidepressant (users) or any exposure considered non-teratogenic (non-users) at the time of the call. Women were excluded if they were also exposed to a known teratogen. Socio-demographic and lifestyles, and medical history were collected during the 1st, 2nd, and 3rd trimesters as well as at 2- and 12-months post-partum by telephone interviews; validated measures of maternal depression (EPDS) were used. Exposure to antidepres-

sants was reported by the mother, and defined by trimester of use, type and dosage. At 12-months of age, children were evaluated at home by a psychometrician using the Bayley-III scales of infant/toddler development. The composite scores (five scales) of the Bayley-III are age-standardized with a mean score of 100 (SD = 15); 80 is the cut-off for delay.

Results: A total of 146 infants were included; 80 had been exposed to antidepressants in-utero (55%). The majority of pregnant women used SSRIs or venlafaxine (87%). Adjusting for maternal depression during and after pregnancy, maternal age and socio-economic status, parity and child's gender, gestational exposure to antidepressants had no significant effect on cognitive, language, social-emotional, and adaptive behavioural development at 12-months old ($p > 0.05$). However, use of antidepressants during pregnancy significantly delayed motor development (OR: 2.61, $p < 0.05$).

Conclusions: We have shown that antidepressant use during pregnancy, especially SSRIs and venlafaxine, was independently increasing the risk of motor delay at 1-year old. Assessments at later stages of life are needed to determine whether this is a long term effect.

65. Validating a Gestational Length Algorithm Based on Administrative Health Plan Data

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Background: Administrative health plan databases are increasingly used in pregnancy research, but data on gestational length (GL) is often not available in these databases.

Objectives: To examine the validity of an algorithm that uses delivery date and preterm birth diagnosis codes to define GL.

Methods: We identified live born deliveries among women aged 15–45 years in 2001–2007 within eight of the 11 health plans participating in the Medication Exposure in Pregnancy Risk Evaluation Program in the U.S. The algorithm assumed specific gestation weeks for deliveries with preterm diagnosis codes or otherwise a 270-day gestation. We compared the GL derived from the algorithm with that obtained from the linked infant birth certificates ("gold standard"). We also compared the prenatal exposure status of two antidepressants (fluoxetine and sertraline; intended for chronic use) and two antibiotics (amoxicillin and azithromycin; intended for short-term use) identified using the algorithm with that determined by the gold-standard GL.

Results: The study population comprised 225,384 deliveries. The mean algorithm-derived GL was lower than the mean obtained from the birth certificates among singleton (267.9 ± 8.3 vs. 273.5 ± 14.3 days), but not multiple-gestation deliveries (253.9 ± 19.0 vs. 252.6 ± 23.1 days). The difference between the two GLs was within ±7 days in 45% of term and 61% of preterm deliveries, and within ±14 days in 77% of both term and preterm deliveries. Among the 146,173 deliveries to women with continuous enrollment and pharmacy benefits from 100 days preceding pregnancy through delivery, the algorithm-derived prenatal exposure to the studied antidepressants had sensitivity and positive predictive value (PPV) ≥96% and specificity and negative predictive value (NPV) close to 100%. The accuracy was slightly lower for the selected antibiotics, with sensitivity and PPV ≥90% and specificity and NPV >99%.

Conclusions: A GL algorithm based on administrative health plan data correctly classified prenatal medication exposure in most deliveries, but exposure misclassification might be somewhat higher for drugs typically prescribed for acute conditions.

66. Use of Non-Steroidal Anti-Inflammatory Drugs and Risk of Miscarriage: A Nested Case-Control Study

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used by pregnant women for pain relief. Previously, we reported association of NSAIDs use and risk of miscarriage but did not account for gestational age.

Objectives: To update earlier analyses, with larger sample, accounting for gestational age.

Methods: Cases were women in northern Denmark suffering first miscarriage in 1998–2010. Using risk-set sampling, we selected up to five controls per case from the pool of women who were pregnant on the index date and whose pregnancies eventually ended in a miscarriage,

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induced abortion, or birth; we matched on conception year and on gestational age at on the index. We ascertained use of on-prescription NSAIDs before the index date from prescription reimbursement records. To evaluate confounding by indication, we examined association of miscarriage with use of paracetamol. To reduce potential reverse causation, we did not include use of NSAIDs on the date of miscarriage in the definition of the exposed condition.

Results: There were 24,333 cases and 120,537 controls. Mean gestational age at index date was 9.3 weeks (standard deviation, 2.9 weeks). Cases were more likely than controls to have used NSAIDs before the index date. The odds ratios (OR) adjusted age at index date, gestational age, calendar year, parity, and maternal use of antiepileptic or antidiabetic preparations were: 2.5 (95% confidence interval [CI]: 1.8–3.5) for last use 1 week before miscarriage; 1.8 (95% CI: 1.3–2.4) for last use 2 weeks before miscarriage; 1.4 (95% CI: 1.1–1.9) for 3 weeks, 1.2 (95% CI: 0.9–1.6) for 4 weeks; and 1.1 (95% CI: 1.1–1.1) for use 5 weeks or more. When paracetamol was substituted for NSAIDS, no association was observed. Furthermore, use of NSAIDs was not associated with induced abortions.

Conclusions: Use of NSAIDs is associated with an increased risk of miscarriage, with evidence that association increases with temporal proximity of drug use to miscarriage. Although reverse causation and unmeasured confounding cannot be ruled out, lack of an association with paracetamol speaks against both.

67. Deriving Propensity Scores for Matching or Stratification in Studies with an Important Subgroup Variable as a Strong Confounder

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Background: In comparative effectiveness research studies, covariate selection is critical in deriving propensity score (PS) to control for confounding. Efficiency can be lost when including covariates related to treatment but not outcomes. However, the effect of covariates on outcomes or treatment may vary by subgroup, and the impact of using an overall PS vs. subgroup-specific PSs is not well known.

Objectives: To assess differences between subgroup-specific and overall PS using a 1:1 PS matching or stratification.

Methods: Patients aged 25–64 with type 2 diabetes at initiation of metformin or sulfonylurea monotherapy between 2003 and 2010 were identified in a US claims database. Confounders and risk factors for acute MI (AMI) were used to derive PS in all patients (overall PS) and within cardiovascular disease (CVD) subgroups (subgroup-specific PS). PS stratification and 1:1 matching were applied with Cox proportional hazard models to analyze time to AMI.

Results: With 1:1 matching in over 92% of patients, baseline covariates were balanced with both overall and subgroup-specific PS, but within prior CVD, balance was better with subgroup-specific PS (average standardized absolute mean difference (ASAMD): 0.0096) than overall (ASAMD: 0.0820). With PS decile stratification, balance was similar with both subgroup-specific PS (ASAMD: 0.0271) and overall PS (ASAMD: 0.0398). HR estimates ($\pm$95% CI) were highly consistent (HR range: 1.1–1.15) between overall and subgroup-specific PS for 1:1 matching, differing by $<1\%$ from crude estimates in those without prior CVD, and only 3–6% respectively, in those with prior CVD. PS stratification showed similar patterns.

Conclusions: If the relationship between covariates and treatment varies by category of a strong confounder, a subgroup-specific PS may better balance covariates within subgroups using PS matching or stratification; however, hazard ratios appear to be relatively consistent in this example of new users of sulfonylurea and metformin monotherapy aged <65 years, suggesting marginal baseline differences or that subtle differences in relationships between covariates and treatment do not affect outcome.

68. Optimal Approaches to One-to-Many Propensity Score Matching in Cohort Studies

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Background: Among the large number of cohort studies that employ propensity score (PS) matching, most match patients 1:1. Increasing the matching ratio to 1:n will generally improve precision but may also increase bias.

Objectives: To evaluate via simulation study several methods of PS matching one treated patient to n untreated patients, and to evaluate differences in bias and variance.

Methods: We simulated cohorts of 20,000 patients with exposure prevalence of 10% to 50%. We simulated five dichotomous and five continuous confounders at varying levels of strength. We created a continuous outcome. We then estimated PSs and matched on PS three ways: (1) using a standard SAS-based greedy matching method; (2) using a newly-implemented exact nearest neighbor matching method; and (3) using a method that extended our nearest neighbor implementation by requiring a treated patient's untreated matches to have alternatively higher

and lower (or lower and higher) PSs. We compared variable- and fixed-ratio matching, as well as a sequential method of creating 1:n matched sets that assigned each treated patient a first untreated match before adding any second untreated patient matches, and a parallel approach in which high quality second matches could be made even if some treated patients had not yet received a first match. We performed 1,000 simulations in each of 240 scenarios. In each scenario, we recorded mean bias, mean variance, and mean squared error (MSE).

Results: Across the scenarios, increasing the match ratio beyond 1:1 generally resulted in slightly higher bias; for variable ratio matching, the increase in bias was generally $<2\%$. Increasing the match ratio also resulted in lower variance with variable ratio matching (reductions of 20% or more), but higher variance with fixed. The parallel approach generally resulted in higher mean squared error but lower bias as compared to the sequential approach. Variable ratio parallel balanced nearest neighbor matching generally yielded the lowest bias and MSE.

Conclusions: We observed that 1:n matching increased precision in cohort studies at a small cost in bias. We recommend employing a variable-ratio, parallel balanced 1:n nearest neighbor approach.

69. Comparison of Propensity-Score-Weighted and -Matched Estimates in a Comparative Effectiveness Study: A Demonstration Using STAR*D Trial Data

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Background: In settings with treatment effect heterogeneity, different propensity score (PS) implementations give different treatment effect estimates. Previous studies of this phenomenon have evaluated unintended adverse effects, unexposed comparator cohorts, and monotonic patterns of heterogeneity only, with treatment apparently protecting people in higher propensity score strata and harming those in lower strata. In the presence of treatment effect heterogeneity, standardized mortality ratio (SMR) weights and matching without replacement can be used to estimate the treatment effect in the treated but give similar estimates only when a match is available for every treated observation.

Objectives: We explored the difference between SMR-weighted and PS-matched estimates in a setting with a non-monotonic pattern of treatment effect heterogeneity and few available matches for treated observations.

Methods: Using subsample data (N = 1,292) from Sequenced Treatment Alternatives to Relieve Depression, a 2001–2004 effectiveness trial of depression treatments, we used PSs to balance treatment groups, compared weighted with matched treatment effect estimates, and assessed sensitivity of the weighted estimates to extreme weights.

Results: The treatment effect showed a U-shaped pattern, with beneficial effects only in the highest and lowest PS strata. Weighted and matched treatment effect estimates differed (weighted RR 1.28, 95% CI 0.97–1.69; matched RR 1.00, 95% CI 0.75–1.34). In sensitivity analyses, as increasing numbers of observations at both ends of the PS distribution were excluded from the weighted analysis, the weighted estimates approached the matched estimate (weighted RR 1.04, 95% CI 0.77–1.39 after excluding, from both groups, observations below the 5th percentile of the treated and above the 95th percentile of the untreated).

Conclusions: Selecting a PS implementation method appropriate for the population of interest is a crucial analytic step. Weighted estimation in particular should include checking assumptions and conducting sensitivity analyses.

70. Use of Confounders' Time Patterns to Improve Bias Adjustment with High-Dimensional Propensity Scores

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Background: Suissa proposed "profile scores," simple-to-calculate values indicating the time pattern of a confounder's occurrence in the period leading up to exposure.

Objectives: We sought to capture and adjust for additional information about patients' severity of condition at baseline via automated generation of profile scores and selection of the scores most likely to improve study validity.

Methods: In a longitudinal database cohort study of the risks of gastrointestinal (GI) bleeding in initiators of coxibs vs. nonselective-NSAIDS, we created profile scores for each patient and for each of thousands of potential confounders. These potential confounders were drawn from recorded diagnostic codes, procedure codes, and drugs dispensed ("recorded codes") over 12 months prior to treatment. The profile scores ranged from 0 (all occurrences of that confounder had taken place a year before exposure) to 11 (all occurrences took place in the month preceding exposure). To focus on pre-exposure variables,

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we created a dichotomous variable that was 1 if the profile score was ≥8.0 and 0 otherwise. Using the high-dimensional propensity score (hd-PS) framework, we combined dichotomous profile scores with hd-PS's standard variable candidates: values indicating presence and frequency of recorded codes for each patient. From >5,000 variables created, we selected the 500 with the strongest potential to add bias to our effect of interest, estimated a propensity score (PS), and used deciles of PS in a model to assess relative risk.

Results: The selected scores included hospitalizations and emergency visits just preceding exposure. The crude odds ratio (OR) was 1.09 with a 95% confidence interval of 0.91–1.30. Adjusting for a propensity score created from 500 variables not including profile scores, we observed an OR of 0.87 (0.71, 1.05). When adjusting for a propensity score created with 500 variables including profile scores, we observed an OR of 0.85 (0.70, 1.03).

Conclusions: Automated inclusion of profile scores incrementally improved the validity of this highly-confounded study. We recommend its routine use as part of the high-dimensional propensity score algorithm.

71. A Comparison of Boosted CART and Logistic Regression for the Estimation of Propensity Scores

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Background: Traditionally, propensity score (PS) estimation involves parametric models, which require strong assumptions about covariate selection and functional relationships between the covariates and treatment. Non-parametric predictive models, in particular boosted classification and regression trees (CART), have been shown to be a valid alternative, but only in specific situations.

Objectives: To gain a general understanding of the relative performance of boosted CART and logistic regression as PS estimation methods under different conditions.

Methods: We conducted simulations with a dichotomous treatment, a Poisson outcome, two confounders, one instrument, and one risk factor. We replicated each simulation scenario with both dichotomous and continuous covariates for sample sizes of N = 1,000, 10,000 and 100,000. Interactions were included in the treatment model to evaluate the performance of boosted regression in modeling the interactions terms and to observe the impact of excluding interaction terms from the logistic model.

Results: Both boosted CART and logistic PS models balanced measured covariates across treatment groups when predictors of treatment were dichotomous. With continuous predictors of treatment, the estimated PSs resulting from boosted CART were biased, thereby failing to balance measured covariates across treatment groups. The percent bias of the effect estimates when using boosted regression was inversely proportional to sample size, ranging from 29% for N = 1,000 to 5% for N = 100,000 when interactions in the treatment model involved two confounders, 21% for N = 1,000 to 3% for N = 100,000 when interactions involved an instrument and confounder, and 25% for N = 1,000 to <1% for N = 100,000 without interactions in the treatment model. Logistic PS models that excluded interactions resulted in effect estimates that were biased by 5% to 15%.

Conclusions: In estimating PSs, boosted CART performs well (as compared to a misspecified logistic model) when covariates are dichotomous or sample size is large. The ability of misspecified PSs to balance treatment groups is, in general, more sensitive when predictors of treatment are continuous as opposed to dichotomous.

72. Evaluating Propensity Score Balance Measures in Typical Pharmacoepidemiological Settings

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Background: Several propensity score (PS) balance measures have been compared in simulated data with normally distributed covariates. Comparisons in data with binary or mixed covariate distributions and rare outcomes, typical of pharmacoepidemiologic data sets, are scarce.

Objectives: To compare balance measures in simulated data with various covariate distributions and rare outcomes.

Methods: We performed Monte Carlo simulations to examine the relative ability of different balance measures to select PS models that yielded the least biased estimates. In different simulations, covariates were binary, normal or gamma distributed, considering sample sizes of n = 400, 1,600, and 3,000, incidence of outcomes of 10% and 25%, and strength of exposure-outcome association of OR = 1 and 2. Bias was estimated as the difference between the true marginal effect and the effect estimate obtained from a logistic regression model with PS as a covariate. The balance of covariates between treatment groups was assessed using the standardised difference (SD), Kolmogorov Smirnov (KS) distance, Lévy distance (Lévy) and overlapping coefficient (OVL). Pearson's correlation coefficients (r) between these balance measures and bias were calculated.

Results: With large sample sizes, all balance measures were similarly correlated with bias irrespective of covariate distributions, strength of the effect, and prevalence of outcome (e.g., when all covariates were binary, OR = 2.0, n = 3,000 and incidence of outcome = 25%: correlations were 0.76, 0.79, 0.79, and -0.79 for SD, KSD, Lévy and OVL, respectively). These correlations decreased with smaller sample sizes (e.g., for n = 400: 0.51, 0.20, 0.17, and -0.43, for SD, KSD, Lévy distance and OVL, respectively). Incidence of the outcome and strength of the exposure-outcome relation didn't have much impact. For sample sizes smaller than 800, SD showed a better correlation with bias than the other balance measures.

Conclusions: The SD or KS performed best across different simulation scenarios and are recommended for reporting the amount of balance reached and selecting the final PS model.

73. Advanced Methods and Measures for Studying Complex Drug Utilization Patterns with Patient-Level Databases

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Background: Drug utilization patterns are studied to identify problems in drug use, such as (non)adherence of prescribers to clinical practice recommendations and (non)adherence of patients to prescribed medication. With the wider availability of (anonymous) patient-level databases with longitudinal data on drug prescribing or dispensing, a range of instruments and measures have become available to better identify and quantify drug use problems.

Objectives: To review concepts, methods and measures used in drug utilization research for indentifying and quantifying complex drug use patterns with patient-level longitudinal data.

Description: Target group: Researchers wanting to gain insight in the opportunities and pitfalls when studying (in)appropriate drug prescribing and drug use using databases with patient-level data.

Description: The symposium will offer 3 presentations focusing on the measurement of specific drug use issues. For each topic, the presenters will give an overview of approaches and instruments that can be used, their underlying concepts, and show examples illustrating the advantages and disadvantages of specific methods and measures. The presentations will cover:

1. studying complex drug utilization patterns at patient level: concomitant drug use, switching patterns, add-on treatment, polypharmacy, dynamic models of drug use (M Andersen and H Wallach Kildemoes);
2. studying prescribing quality with patient-level data: classification of measures according to quality aspects, drug vs. disease oriented prescribing indicators, cross-sectional and sequential assessment, validity of different types of prescribing quality indicators (P Denig and L Pont);
3. refill-adherence measures using prescription and dispensing data: persistence vs. compliance measures, medication possession ratio and gap-methods, correction for intermittent use and stockpiling, strengths and weaknesses of different types of data (J Voorham and JP Gregoire).

Each presentation will be followed by a short round of questions and discussion, and at the end a summary of the key messages will be given by the chair from the Special Interest Group in Drug Utilization/Health Services.

74. Biases To Consider When Studying the Risk of Medication Use in Pregnancy

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Background: Studying the association between medications and adverse pregnancy outcomes is challenging, and subject to a number of different biases.

Objectives: To discuss common selection, information and confounding biases encountered when studying the safety of medications during pregnancy. Researchers involved in or seeking knowledge about studying adverse pregnancy outcomes would benefit from attending this session.

Description: In this SiG MiP sponsored symposium, we will review possible sources of bias that can be present and should be taken into account in the design, analysis, and interpretation of the results of medications in pregnancy studies. Since certain types of selection and information biases differ between study designs, we will discuss how these biases specifically affect pregnancy registries, pregnancy cohorts in automated health care databases, and case-control studies. In addition, we will review the concept of confounding in the context of pregnancy outcomes and discuss which factors should be adjusted (e.g., maternal age, indication) and which factors might not have to be adjusted for (e.g., birth weight). The speakers will address and present examples of biases. The session will include a 15 minutes presentation by each speaker, followed by approximately 20 minutes of discussion open to the public. At the end of the symposium the attendees should have a good overview of the possible biases that

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should be taken into account when studying the safety of medications in pregnancy.

Talks will cover: 1. introduction to bias and confounding;

2. biases in pregnancy registries and studies from Teratology Information Services;
3. biases in studies using data from birth defects registries;
4. biases in studies using administrative databases;
5. confounding bias.

75. Databases, Biologics, and Biomarkers: The Challenges and Rewards of Incorporating Biological Specimens in Pharmacoepidemiologic Research

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Background: In the new era of biological therapy and personalized medicine, translational research in drug development have led to a greater need to study biological specimens for potential predictive biomarkers of toxicity (pharmacovigilance) and (comparative) efficacy. Pharmacoepidemiologists, by virtue of their expertise in coordinating data collection in observational studies, play a key role in the coordination of biological specimen collection, and in the subsequent analyses.

Objectives: Objective 1.

First hour: To provide successes and challenges of how biological specimens were incorporated into the following types of study designs and databases, leading to changes in clinical practice: (1) secondary analysis of existing databases from either randomized control trials or Phase IV observational studies from industry, cooperative groups, and academic settings; (2) prospective multi-institutional networks with rapid case identification; (3) large observational databases (e.g., Health Maintenance Organizations, Government supported population studies).

Dr. Wilson will present a 15-minute, top 10 problems she encountered in this field. The next three speakers will present 15 minute presentations that highlight successes and challenges related to their projects.

Objective 2.

Last half-hour: To discuss the real challenges involved with setting up biospecimen collection, alongside practical strategies to overcome such challenges. The formal will be a directed panel discussion, led by the SIG representatives.

We have had great success and strong participation using this particular format at a recent NIH-sponsored meeting. This Symposium will straddle the interests of multiple ISPE SIGs, including Pharmacogenetics and Molecular Epidemiology, Biologics, Databases, Pharmacovigilance, and Comparative Effectiveness.

76. How to Conduct Collaborative Studies in the EU? Lessons and Results from the Completed Safety of NSAIDs (SOS) Project

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Background: After a formal review procedure of the safety of coxibs. The European Medicines Agency realized that similar data were missing for the traditional NSAIDs. The SOS project was funded through the European Commission to assess and compare the risk of cardiovascular and gastrointestinal events of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with the ultimate goal of providing decision models to clinicians and regulatory authorities. This was done with a unique and revolutionary strategy for the EU. The strategy consisted of meta-analyses of published clinical trials and observational studies, identification of knowledge gaps followed by a multi-country collaborative observational drug utilization and association study in seven health care databases in the UK, Netherlands, Germany and Italy. The total source population extended beyond 35 million individuals. This workshop will share the lessons learnt from this project, compare literature meta-analysis with individual patient level analysis, and collaborative studies, and reveal some of the newest findings on NSAID safety.

Objectives: To share and discuss approaches to collaborative studies in EU databases and to the recognize the challenges and opportunities.

Description: The workshop will focus on some of the most important lessons that have been learned during the SOS project and will be decorated with some of the newest results. The workshop will feature the following topics and speakers:

1. What can we learn about NSAID safety from clinical trials?
2. What can we learn about NSAID safety from existing observational studies? What are the knowledge gaps?
3. How can we map and bridge across different databases and health care structures in the EU?

4. How can assure homogeneity in outcome and co-variate extractions?

5. How to work and analyse together? The SOS Datawarehouse.

6. Integration of data through a personalized risk prediction model and clinical decision models.

7. How to communicate with the different stakeholders?

77. Improving the Science of Regulatory Decision-Making – Advances in 2011/2012

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Background: The FDA and other regulatory agencies are paying increased attention to advancing regulatory science. In 2010 the NIH and FDA launched the Advancing Regulatory Science Initiative and awarded $9.4 million (3 years) to support four research projects in regulatory science. Most efforts to develop drug regulatory science address drug development and postmarketing benefit/risk assessment. However, they frequently fail to address how better data will be translated into decision making. Last year, this panel of international experts held a workshop and elucidated the challenges and efforts to improve the science. Several regulatory initiatives have been launched in 2011 and 2012, as well as new academic programs.

Objectives: 1. To understand the scope of current US and non-US efforts to improve regulatory science, particularly those that have been launched in the past 12 months.

2. To discuss how these efforts are addressing scientific approaches to regulatory decision-making.

3. To understand how scientific evidence, medical practice, patient preferences, economics, politics, the press, public opinion and other societal considerations affect regulatory decisions.

4. To become familiar with possible scientific approaches to regulatory decision-making.

Description: In Chicago, Drs. Dal Pan (FDA), Raine (MHRA), Leufkens (University of Utrecht) and Avorn (Harvard) reviewed current efforts to improve regulatory science and to move beyond improving the prompt and efficient availability of reliability scientific intelligence to addressing the science of decision-making.

The panel will re-convene to address the question of whether there has been progress in addressing issues of regulatory decision-making since the 27th ICPE. Have the new initiatives, particularly those in the US and Europe improved the decision-making process? How have economic pressures, political pressures, societal preferences, etc. been integrated into regulatory decision-making? What are the major challenges we are currently facing and are there tools being developed to improve regulatory decision-making.

Workshop participants will be encouraged to actively contribute to the discussions.

78. Medicare Part D Data: Will the US Population-Based Data Be Advancing Pharmacoepidemiology and Public Health?

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Background: Medicare Part D is a federal program to subsidize the costs of prescription drugs for Medicare beneficiaries (essentially everyone aged 65 and older) in the United States. It was enacted as part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 and went into effect on January 1, 2006. Linked Medicare Parts A (inpatient), Part B (outpatient), and Part D (dispensed prescription drugs) claims became recently available for research. Linked "Medicare Part D data" is a very large, population-based, US national healthcare database with strong potential for pharmacoepidemioly worldwide.

Objectives: The goal of the symposium is to introduce pharmacoepidemiologists to the unique advantages and limitations of Medicare Part D data for pharmacoepidemiologic research and provide guidance on practical issues related to data purchase and use for various pharmacoepidemiologic projects.

Description: The PPC proposes this symposium on a very timely issue, i.e., the practical consequences of the availability of the first US population-based healthcare database including dispensed medications (Medicare Part D) for pharmacoepidemiolgic research in older adults (65 years or older). We propose short presentations from various stakeholders followed by a podium discussion. While the data source is US specific, we intend to discuss issues of data access from various angles, including academic vs. non-academic and US vs. international users. The symposium will focus on practical issues around purchase and data use agreements including issues related to updating data over time (necessary to achieve intimate knowledge of data advantages and limitations), availabil-

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ity for various constituents of ISPE, and use for sponsored pharmacoepidemiologic research projects.

79. Unique Device Identification System (UDIS): Implications for Postmarketing Safety and Effectiveness Assessment in the United States and Europe

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Background: Compared to medications, unique gaps exist in the accumulation and appraisal of premarket safety and efficacy evidence for medical devices. These gaps require adequate infrastructure and methods to study safety and effectiveness of medical devices for real world patients in the postmarket setting. The evolving UDIS will capture device information in various data sources and transform national and international capabilities for efficient and high-quality adverse event reporting, postmarket surveillance and comparative effectiveness studies, and recall management for medical devices.

Objectives: To review the current status of the development of a global UDIS, discuss challenges and implications of implementation in clinical practice and data collection, and consider the ramifications of a UDIS for medical device safety and effectiveness research.

Description: The symposium will consist of didactic presentations, followed by a panel discussion (presenters/moderators shown by initials).

1. Overview of the UDIS: Current status, vision, and FDA's perspective (JC; 12 minutes).
2. Adverse event reporting and the UDIS: How the UDIS will enable manufacturers to optimize proactive and timely signal detection (MS; 10 minutes).
3. Implementation of the UDIS: Vision and challenges in implementation of the UDIS (AS; 10 minutes).
4. Practice of device-epidemiology and the UDIS: Opportunities and challenges for device safety and effectiveness research in the era of UDIS (SS; 10 minutes).
5. European registries and the UDIS: EU requirements for UDIS implementation and challenges and solutions for German registries (GL; 10 minutes).
6. Toward Safe and Effective Use of Medical Devices - MDEpiNet-: How a recently launched FDA initiative, Medical Device Epidemiology Network (MDEpiNet) will advance methodologies and infrastructures for device epidemiology and surveillance through Public Private Partnership between the government, academia, industry and other stakeholders. (DMD; 8 minutes).
7. Panel Discussion: Integrating the UDIS into the toolkit for postmarket surveillance, monitoring, and evaluation (Panelist: all speakers, Moderators: MBR and JJ; 30 minutes).

80. The Effect of Air Pollution on Anemia and Response to Treatment with Erythropoiesis Stimulating Agents in Dialysis Patients

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Background: Many patients with an anemia of end-stage renal disease exhibit a poor response to treatment with erythropoiesis stimulating agents (ESAs) because of chronic inflammation.

Objectives: To examine whether patients living in areas with high levels of ambient particulate matter, a proinflammatory exposure, exhibit worse anemia or decreased ESA responsiveness.

Methods: We geocoded all US dialysis units and used established geospatial air pollution models to predict the average annual PM10 concentration at each facility. We then identified a cohort of patients who started dialysis between 1995 and 2005 and survived until 9 months after the start of dialysis. For these patients, we extracted the first available ESA claim and hematocrit measurement. Using multivariable linear models controlling for calendar year, patient, and facility characteristics, we modeled baseline hematocrit and ESA dose and hematocrit at 9 months as a function of predicted PM-10 concentration at the facility where the patient was treated.

Results: We identified a cohort of 287,385 patients who met entry requirements. After multivariable adjustment, we found that a 100 $\mu g/m^3$ increase in PM10 was strongly associated with decreased baseline hematocrit (-2.5%, 95% CI -2.8 to -2.0), but weakly associated with decreased hematocrit at 9 months (-0.4%, 95% CI -0.7 to -0.1), and unassociated with ESA dose at 9 months (30 units/day, 95% CI -100.0 to 170).

Conclusions: Patients beginning dialysis in areas with high PM10 concentrations are more anemic but exhibit only a very slightly diminished response to treatment with ESAs.

81. How Much Are Biosimilars Used in Southern Italy? A Retrospective Analysis of Epoetin Utilization in the Local Health Unit of Messina in the Years 2010–2011

Gianluca Trifirò,[1] Carmelina Sgroi,[2] Salvatore Coppolino,[2] Rosarita Ferrara,[1] Vincenzo Arcoraci,[1] Pasquale Cananzi,[3] Vincenzo Savica,[1] Martijn Schuemie,[4] Achille P Caputi.[1] *[1]University of Messina, Messina, Italy; [2]Local Health Unit of Messina, Messina, Italy; [3]Health Assessorate of Sicilian Region, Palermo, Italy; [4]Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: Epoetins are one of the three biologics for which biosimilars are available in Italy since 2007. So far, there is lack of Italian national/regional longitudinal data about epoetin use.

Objectives: To evaluate the prescribing pattern of epoetins in a Local Health Unit (LHU) of Southern Italy in the years 2010–2011.

Methods: A retrospective drug utilization study was conducted during the period January 1st, 2010–May 31st 2011. Data source was the dispensing database of LHU of Messina, which contains anonymised data about dispensed drugs that are prescribed by specialists to residents in the catchment area. Indication of use and prescribed dosage of epoetins is derived from therapeutic plans filled by specialists. Prevalence and volume of use (DDD/1,000 in h/day) as well as expenditure of epoetins in the province of Messina (653,810 in hour) in 2010 was calculated. Frequency analyses by sex, age, indication of use of epoetin users were performed. Switching pattern between different reference product and biosimilar epoetins was explored.

Results: Overall 4,288 patients (mean age ± SD: 74.2 ± 13.7) were treated with epoetins during the study period. Darbepoetin alpha and reference product epoetin alpha accounted overall for 79.8% of epoetin users, while biosimilars of epoetin alpha for 0.9%. Overall, 85.4% of epoetin users were treated because of anemia due to chronic kidney disease (CKD) and 158 (12.6%) because of chemotherapy-induced anemia. In 2010, prevalence of use of epoetins was 5.5 (95% Confidence Interval: 5.3–5.7) per 1,000 inhabitants in the province of Messina. The volume of use and related expenditure for epoetins was 3.58 DDD/1,000 inhabitants/day and 5,572,457 € (about 8.5 € per capita/day) in 2010. Switching between different epoetins was very frequent (21.8% of users) but was very rare from reference products to biosimilars.

Conclusions: Epoetins are frequently dispensed in LHU of Messina mainly due to CKD-related anemia. Switching between different epoetins is very common. Use of biosimilars is very low in both naïve patients and switchers from reference product epoetins.

82. Utilization Pattern of Golimumab (Simponi®) in Patients with Inflammatory Arthritis in Real-Life Clinical Practice in Canada

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Background: Golimumab (GLM) is a subcutaneous tumor necrosis factor-alpha inhibitor that is indicated for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). The recommended posology of GLM is 50 mg subcutaneously once a month.

Objectives: The purpose of this study was to evaluate GLM dosing patterns in real-life clinical practice in Canada.

Methods: A retrospective longitudinal cohort analysis was performed using the IMS Brogan private drug plans database. This database is comprised of pay direct drug benefit claims paid by most major private insurers in Canada. The study timeframe was from January 1, 2009 to June 30, 2010. Patients were included if they had ≥3 claims for GLM between January 1, 2009 and December 31, 2009. The 6-month period preceding the first GLM claim (index date) for each patient was used as a baseline to determine any prior biologic use. The 12-month period following initiation of GLM was used to assess dosing patterns. For each patient, GLM weekly doses and dosing intervals were calculated for every dosing episode (defined as the time-interval between two consecutive claims).

Results: A total of 397 patients receiving at least three prescriptions for GLM were identified as meeting the inclusion criteria. The sample was predominantly female (56%); had rheumatoid arthritis (RA; 76%; n = 303) and mean age of 47 years. Approximately 49% of patients had no history of biologics prior to GLM initiation (bio-naïve) while 51% were bio-experienced. The average monthly dose of GLM was 50 mg. The mean ± SD and median dosing interval were 32 ± 8 and 31 days, respectively. Dosing intervals were similar among bio-naïve and bio-experienced patients.

Conclusions: In this retrospective cohort analysis, most patients with a prescription for GLM were female, had a diagnosis of RA, and half of patients had prior treatment with biologic therapies. The majority of GLM prescriptions were 50 mg with a median dosing interval of every 31 days. Real-world dosing patterns of GLM corroborated the recommended posology of one 50 mg injection once monthly; they were similar among bio-naïve and bio-experienced patients.

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83. Malignancy and Infection Rates in Psoriasis Patients with or without Treatment and in a General Population in the US: 2005–2009

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Background: There are limited comparable data on rates of malignancies and hospitalized infectious events (HIEs) in psoriasis (PsO) patients (pts) and among PsO pts on specific treatments (txs).

Objectives: We assessed the incidence of malignancies and HIEs in a general population (GP), a PsO population (pop'n), and PsO pop'ns prescribed specific txs within a large US health-insured pop'n.

Methods: Using an administrative claims database, we identified a GP (N = 18,094,518) and a cohort of PsO (ICD-9 code 696.1) pts aged ≥18 years between 1/1/06 and 12/31/06 followed through 12/31/09 to assess incidence of malignancies (lymphoma, non-melanoma skin cancer (NMSC), all cancers excluding NMSC) and HIEs. PsO pts prescribed the following txs for ≥1 dose after diagnosis (dx) were exposed to that tx: non-biologic (NB) systemics (methotrexate, cyclosporine), phototherapy (PUVA, UVB), other TNF blockers (adalimumab, infliximab), and etanercept. Follow-up ended at first dx of an outcome event, loss to follow-up, or completion of 3 years of follow-up. For HIEs, follow-up also ended 30 days after tx discontinuation or switch. Age- and sex-standardized incidence rates and 95% confidence limits were calculated.

Results: Among 40,987 PsO pts, 11% were prescribed NB, 6.2% other TNF blockers, 15% etanercept, and 11% phototherapy. Some pts were prescribed more than one tx. For all cancers, lymphoma, and NMSC, the incidence rates per 10,000 person-years for the PsO cohort were significantly elevated compared to the GP (all cancers: 114 (95% CI: 107–121) vs. 95 (95% CI: 95.0–95.6); lymphoma: 9.4 (95% CI: 7.4–11.4) vs. 5.8 (95% CI: 5.8–5.9); NMSC: 129 (95% CI: 121–136) vs. 78 (95% CI: 77.7–78.3)]. For the four tx groups, small differences were shown in incidence of all cancers and lymphoma from the GP but NMSC rates were higher in each. HIE rates were higher in the three systemic tx PsO groups relative to the phototherapy group.

Conclusions: Incidence rates of malignancies are elevated in PsO pts compared to the GP. Rates of malignancies and HIEs vary by tx, suggesting that risks from both tx and the underlying disease must be taken into account to understand tx-related risks.

84. Utilization of Tumor Necrosis Factor alpha Inhibitors (TNFi) in Patients with Ankylosing Spondylitis

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Background: TNFi is an important treatment option for ankylosing spondylitis (AS). Upon incomplete efficacy response or occurrence of adverse events, patients may either discontinue TNFi therapy or switch to a second TNFi.

Objectives: To describe the utilization pattern of TNFi in US patients with AS.

Methods: A descriptive analysis was performed using the Ingenix LabRx claims data between January 1, 2000, and June 30, 2010. Patients between 18 and 64 years old with AS diagnosis (ICD-9 code 720.xx) were included if they newly initiated TNFi therapy and had at least 6 months continuous enrollment prior to the initiation date. TNFi use was identified by the national drug code and the health care common procedure coding system J-code entered on claims. Eligible patients were followed through the discontinuation of TNFi therapy, first TNFi switching, or the end of continuous enrollment, whichever came first.

Results: A total of 152,200 AS patients were identified, and 7,103 AS patients had at least 1 TNFi claims. The final analysis included 3,408 patients that met all the selection criteria. The median follow up time was 1.9 year (IQR: 0.85–3.8). Etanercept was the most often used initial TNFi during the entire study period (51.6%). However, initial use of adalimumab increased dramatically since 2003, and exceeded etanercept in 2009 (48.7% vs. 31.1%). Since only 43 (1.3%) patients started TNFi therapy with golimumab or certolizumab pegol, they were excluded from further analysis. The age, gender, and baseline rheumatic drug utilization were similar among etanercept, adalimumab, and infliximab initiators. During the follow-up time, 1,016 (30.2%) patients discontinued TNFi therapy, and 595 (17.7%) patients switched to a second TNFi. Infliximab initiators had the best persistency. Their median times before discontinuation and switching were 235 days (IQR: 132–579) and 475 days (IQR: 240–841), respectively.

Conclusions: The prevalent use of TNFi is about 5% among AS patients in US. Adalimumab appears the most popular initial TNFi in recent years. Infliximab has better persistency than adalimumab and etanercept.

85. A Comparison of Post-Authorization Adverse Events of Biopharmaceuticals and Small Molecules within the Same Anatomical Therapeutic Chemical Class

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Background: The nature of adverse events (AEs) observed post authorization for biopharmaceuticals differs from chemically synthesized, small molecules. It remains unclear if this observed difference can be attributed to differences in authorized indications between the groups.

Objectives: To investigate if the nature of AEs identified post-authorization for biopharmaceuticals differs from AEs of small molecules within the same Anatomical Therapeutic Chemical (ATC) class.

Methods: All biopharmaceutical and small molecule products centrally approved in the European Union classified in the ATC class of "antineoplastic and immunomodulating agents" ("L") were included. Generics and biosimilars were excluded. All safety related changes to the Summary of Product Characteristics during 2004–2011 were analyzed; individual AEs were identified and coded according to MedDRA 14.1. Proportions of AEs within therapeutic subgroups were compared and tested using two-sided Fisher's exact tests.

Results: A total of 747 AEs were identified; 361 for biopharmaceuticals and 386 for small molecules. For biopharmaceuticals, 171 (47.4%) AEs were reported for immunosuppressants, 128 (35.5%) for immunostimulants and 62 (17.2%) for antineoplastic agents. For small molecules the most AEs, 288 (74.6%), were reported for antineoplastic agents, 92 (23.8%) for immunosuppressants and 6 (1.6%) for endocrine therapies. Within the ATC subgroup of immunosuppressants, neoplasms, 20% vs. 2% ($p < 0.01$) and infections and infestations, 22% vs. 9% ($p < 0.01$) occurred significantly more frequent for biopharmaceuticals. AEs of small molecules were more often renal and urinary disorders, 7% vs. 0% ($p < 0.01$), blood and lymphatic system disorders, 10% vs. 3% ($p = 0.04$) and vascular disorders, 7% vs. 1% ($p = 0.02$). In the sub group of antineoplastics, immune system disorders occurred more frequently for biopharmaceuticals, 6% vs. 1% ($p = 0.04$).

Conclusions: The distribution of AEs identified post authorization differs for biopharmaceuticals and small molecules, even in products from the same therapeutic subgroup. This may warrant a targeted pharmacovigilance approach for biopharmaceuticals.

86. Drug-Related Progressive Multifocal Leukoencephalopathy (PML): Data Mining of FDA_AERS (Adverse Event Reporting System)

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Background: In the last decade, regulatory agencies issued warnings on the risk of PML for various immunosuppressant drugs, in particular Monoclonal Antibodies (MAbs).

Objectives: To identify drug classes with a statistically significant signal of PML through the spontaneous adverse event reporting analysis.

Methods: A case/non case study of all reports collected in the FDA_AERS in the period 2004–2010 was performed. After duplicate removal and drug mapping by Anatomical and Therapeutic Chemical (ATC) classification, all drug-report pairs for "suspected" or "interacting" drugs were selected. Drugs with ATC codes L01-Antineoplastics, L04-Immunosuppressants and H02-Corticosteroids were defined "Immunosuppressants" and, among these, MAbs were identified. Cases were represented by the reports including MedDRA preferred term "Progressive multifocal leukoencephalopathy"; non-cases were all reports of other reactions. Reporting Odds Ratio (ROR) with 95% confidence intervals (95% CI) was calculated for overall immunosuppressants, for MAbs group and, finally, for each MAb.

Results: Among 2,019,944 reports concerning 2,768,764 drug-report pairs, we retrieved 980 reports of PML corresponding to 2,139 drug-report pairs. A statistically significant ROR was found for immunosuppressants (ROR: 1.87; 95CI%: 10.73–13.12); within this therapeutic class, ROR was statistically significant for MAbs (1.51; 1.37–1.67) rather than for non-MAbs. Among MAbs, disproportionality analysis resulted in a signal for rituximab (16.04; 13.65–18.84), natalizumab (2.72; 2.30–3.21) and alemtuzumab (3.54; 2.29–5.49).

Conclusions: The analysis confirmed an association between PML and immunosuppressants, and it found a stronger disproportionality signal for MAbs rather than other immunosuppressants. Among MAbs, only rituximab, natalizumab and alemtuzumab resulted in a statistically significant ROR, probably affected by the notoriety bias. However, the presence of a signal for MAbs, should call for a more intensive safety monitoring of these drugs. Further studies should investigate the role of underlying disease in the PML occurrence (e.g., deficiency of immune system in lymphoma condition).

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87. Case Definition for Progressive Multifocal Leukoencephalopathy Following Treatment with Monoclonal Antibodies

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Background: Novel immunosuppressive/modulating therapies with monoclonal antibodies (MABs) have been associated with progressive multifocal leukoencephalopathy (PML), a potentially fatal disease of the human brain caused by the JC virus (JCV). Taking the complex diagnostic testing and inconstant clinical presentation of PML into account, an agreed case definition for PML is a prerequisite to allow a thorough assessment of PML.

Objectives: The objective was to develop a standardized case definition for PML following treatment with MABs in order to enhance data comparability across different clinical trials, post-authorization safety studies, and passive post-marketing surveillance. The case definition was aimed to define levels of diagnostic certainty of reported suspected PML cases.

Methods: An interdisciplinary working group was established to develop a PML case definition based on experience in diagnosis/treatment of PML, experience in case assessment for regulatory purposes, review of literature, and group consensus. The case definition was subsequently evaluated against all suspected PML cases following MAB-treatment reported from Germany to the Paul-Ehrlich-Institute (PEI) as the responsible national regulatory authority.

Results: The algorithm of the PML case definition is mainly based on clinical symptoms, polymerase chain reaction for JCV DNA in cerebrospinal fluid, brain magnetic resonance imaging, and brain biopsy. One hunderd and nineteen reported suspected PML cases following MAB-treatment (including natalizumab, rituximab, alemtuzumab, efalizumab, and ofatumumab) were assessed against the case definition. It could be demonstrated that the case definition can be used for case ascertainment for suspected cases of PML for various MABs covering a broad spectrum of indications. Even in case, that the available information is not yet complete, the case definition provides a level of diagnostic certainty.

Conclusions: The proposed case definition enables data comparability among different medicinal products and among active as well as passive surveillance settings. It may build a basis for meaningful risk analysis and communication for regulators and health care professionals.

88. Incidence of Infections, Cardiovascular, and Hepatic Events among Initiators of TNF-α Inhibitor Therapy Compared to Methotrexate Users

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Background: TNF-α inhibitors are often used for the treatment of rheumatoid arthritis (RA) after traditional disease modifying anti-rheumatic drug (DMARD) therapies have failed, yet their effect on select medical conditions needs further study.

Objectives: To perform a hypothesis generating study to determine if initiators of TNF-α inhibitor therapy who have failed treatment with methotrexate (MTX) differ with regards to the incidence of infections, cardiovascular, and hepatic events compared to patients who respond to MTX.

Methods: US medical claims data from 2004 to 2010 were used to identify a cohort of adult RA patients who initiated TNF-α inhibitor therapy after failed treatment with MTX. Patients were matched 2:1 by age, gender, and insurance status to TNF-α naïve MTX-users, and followed for 1 year.

Results: We identified 2,950 RA patients who initiated TNF-α inhibitor therapy after failure with MTX, of which 2,400 were successfully matched with MTX responders. Incident infections and parasitic diseases were more common in patients who initiated TNF-α inhibitor therapy (RR = 1.33). Specific infection groupings with an increased incidence among TNF-α inhibitor initiators included bacterial infection; skin and subcutaneous tissue infection; and other lower respiratory diseases. A lower incidence was observed for other infections including parasitic and intestinal infection. The incidence of cardiovascular events such as thromboembolism and acute cerebrovascular disease were lower among TNF-α initiators (RR = 0.88 and 0.69 respectively); whereas acute myocardial infarction showed no difference (RR = 1.05). Diseases of the liver were more frequent among TNF-α initiators (RR = 1.22).

Conclusions: We observed variable relationships for infections and cardiovascular events and an increased incidence of liver disease among TNF-α initiators compared to TNF-α naïve MTX-responders. Future hypothesis-testing studies are needed to understand the role that TNF-α inhibitors may play in these relationships.

89. Characteristic Differences among Crohn's Disease Patients Who Initiated IFXliximab vs. Non-Biologic Therapy – ENCORE Registry

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Background: Understanding the characteristic differences in patients with Crohn's disease (CD) initiating biologic therapy vs. receiving non-biologic therapies will be helpful for the evaluation of product effectiveness and safety in clinical practice.

Objectives: To describe baseline characteristic differences in patients with CD who initiated Infliximab (IFX) vs. non-biologic therapies.

Methods: The European National Crohn's Observational Registry (ENCORE) is a prospective, observational, post-marketing safety surveillance registry of patients with active or fistulizing CD treated with IFX. Patients on non-biologic therapies were also included as controls. Patients enrollment from gastroenterology practices in 9 EU countries began in 2003 and ended in 2008. Demographic, disease history and other data were collected from patients and physicians at enrollment. Descriptive analyses were conducted to compare baseline characteristics between patients initiated IFX and receiving non-biologic therapies. Differences between the groups were also examined according to year of enrollment and EU region.

Results: ENCORE enrolled 2,664 patients: 1,543 received IFX and 1,121 received non-biologic therapy. Age and gender distribution were comparable between the two groups. However, at baseline CD was more severe in IFX patients than controls, as indicated by higher Harvey-Bradshaw total score (8.19 vs. 6.17, $p < 0.0001$), more draining fistula (22.6% vs. 8.6%, $p < 0.0001$), and more days in hospital in past 6 months. Patients on IFX reported a worse overall health status compared to controls (assessment score of 4.34 vs. 3.87 on a scale of 1–7, $p < 0.0001$), more work days missed due to CD in past 6 months (24.4 vs. 18.4 days, $p < 0.001$), more impact on self-reported work productivity and regular daily activities. Patients who initiated IFX in 2007–2008 seemed to have less severe disease than those initiated in 2003–2004. Patients who initiated IFX in Northern EU seemed to have more severe disease than those in Southern EU.

Conclusions: Patients who initiated IFX differ from those on non-biologic therapy by having more severe disease and more impact on work and daily activities

90. Incidence of Selected Opportunistic Infections among Children with Juvenile Idiopathic Arthritis

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Background: There may be an increased risk of opportunistic infections (OI) among children with juvenile idiopathic arthritis (JIA), especially with exposure to immunosuppressant medications. No controlled studies to address this question have been published to date.

Objectives: We determined incidence rates (IR) of selected OI among children with and without JIA and examined the effects of immunosuppressant medications.

Methods: Using U.S. national Medicaid claims data from 2000 to 2005, we identified a cohort of children with JIA and a non-JIA comparator cohort diagnosed with attention deficit hyperactivity disorder. All subjects had a 3 month baseline period to assess for prevalent OI (which excluded subjects from analysis) and current medication exposures. Incident OI were identified using physician diagnosis or hospital discharge codes and, for some OI, dispensed antimicrobial medications. We standardized the non-JIA IR to the age, sex, and race distribution of the JIA cohort.

Results: The JIA cohort included 8,503 children with 14,370 person-years of follow-up; 1,392 used TNF inhibitors (TNFi) and 3,491 used methotrexate (MTX) during follow-up. The non-JIA comparator cohort included 360,362 children with 490,939 person-years of follow-up. When all OI were considered together as a single outcome, there were 42 OI in the JIA cohort (IR 300 [216–406] per 100,000; incidence rate ratio (IRR) 2.4 [1.7–3.3] vs. non-JIA comparator). We identified three infections with *Coccidioides* (IR 21 per 100,000; IRR 101 [8.1–5,319] vs. non-JIA comparator); five with *Salmonella* (IR 35 per 100,000; IRR 3.8 [1.2–9.5]); and 32 with herpes zoster (IR 225 per 100,000; IRR 2.1 [1.4–3.0]). Among children with JIA, herpes zoster was not strongly associated with current use of glucocorticoids (GC) (IRR 1.8 [0.6–4.5] vs. no current GC use), MTX (IRR 1.4 [0.5–3.6] vs. no current MTX or TNFi use), or TNFi (IRR 2.2 [0.7–6.9] vs. current MTX use without current TNFi use).

Conclusions: OI are rare among children with JIA. Nevertheless, children with JIA had double the rate of OI compared to children without JIA. Herpes zoster was not strongly associated with specific medications used to treat JIA.

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91. Methods to Link a National Arthritis Cohort with Medicare Administrative Claims Data

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Background: While all data sources have strengths and weaknesses, linked clinical and claims data may provide a valuable resource for pharmacoepidemiologic research.

Objectives: To describe methods and validity of a linkage between a national arthritis registry to U.S. Medicare data.

Methods: Data from 2006 to 2009 for rheumatoid arthritis (RA) patients participating in the Consortium of Rheumatology Researchers of North America (CORRONA) was linked to Medicare data (100% sample of enrollees selected using ICD-9 codes for RA or other inflammatory arthritides). In Medicare data, observable person-time was limited to part A + part B months without enrollment in Medicare Advantage. Potentially linkable CORRONA participants were restricted to those who self-reported Medicare coverage and with ≥2 visits to a CORRONA provider. Deterministic linkage was performed using multiple non-unique variables including year of birth, gender, provider ID, and dates of CORRONA-provider office visits. Linkage validity was evaluated in a subcohort of CORRONA with more complete information (e.g., full date of birth).

Results: In Medicare, 73,782 RA and inflammatory arthritis patients had visit(s) with CORRONA providers. A total of 8,149 CORRONA participants with self-reported Medicare coverage for at least two CORRONA visits were potentially linkable. Of these, 7,144 linked to at least one Medicare beneficiary with ≥2 visits occurring in Medicare-observable person time, with exact match on ≥1 visit date. A total of 3,869 CORRONA patients linked on every visit that occurred in both CORRONA and Medicare data (median visits = 5; IQR 3, 8). A total of 3,854 patients linked uniquely (i.e., 1:1 linkage); 15 patients linked non-uniquely. In the validation subcohort, 335 CORRONA patients had ≥2 visits while Medicare enrolled. Among these, 253 linked uniquely; two linked non-uniquely. Linkage accuracy was 86% for patients with only two visits and 96% for patients with ≥3 visits. Ongoing work will refine the linkage strategy and expand the validation sample.

Conclusions: Linkage between a national outpatient arthritis registry and U.S. Medicare claims data using multiple, non-unique identifiers appears feasible and valid.

92. Rates of Systemic Adverse Events Following Intravitreal Injection of Anti-VEGF Medications for the Treatment of Age-Related Macular Degeneration (AMD)

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Background: Intravitreal injections are given for neovascular AMD. Off-label use of bevacizumab (bev) is the most common drug injected intravitreally.

Objectives: To compare systemic adverse events between AMD patients treated with bev or ranibizumab (ran).

Methods: Beneficiaries treated for AMD were identified in Medicare fee-for-service data (2005–2009). Drugs were classified as "Known" (drug-specific billing code) and as "Presumed" (unclassified drug codes and charges). Known and presumed were combined to create an "Any" treatment cohort. Two pre-specified and two post hoc pairs of cohorts were compared: Pre-specified included "Known" patients initiating treatment in 2006–2009 and "Any" patients initiating treatment in 2006–2009. Post-hoc groups included Known 2008–2009 and Any 2008–2009. For each cohort, we examined the relationship between drug and incidence of cerebrovascular events (CVA), myocardial infarction (MI), and all-cause mortality. Cox proportional hazard models, adjusted for demographics, US region, propensity score, and baseline comorbidities, were used to compare risks.

Results: All-cause mortality rates ranged from 5.5 to 7.4 per 1,000 person years (py). In both Known cohort comparisons, risk of all-cause mortality was higher among bev users (hazard ratios (HR) and 99% confidence intervals (CI): 1.11 (1.01–1.23) for Known 2008–2009 and 1.19 (1.10–1.29) for Known 2006–2009). Incidence of hemorrhagic CVA ranged from 0.24 to 0.43 per 1,000 py. Risk of hemorrhagic CVA was also higher in both Known cohort comparisons (HR and 99% CI: 1.57 (1.03–2.36) and 1.43 (1.00–2.03), respectively). However, no statistically significant differences were seen for either of these events in the Any cohort comparisons. No statistically significant differences were seen for MI and ischemic CVA.

Conclusions: Results suggest a potential increased risk of all-cause mortality and hemorrhagic stroke among patients using bev, but does not show an increased risk of MI or ischemic stroke. Practitioners and patients should discuss the risk-benefit profile of treatments and the

strengths and limitations of existing data when selecting a treatment.

93. Measuring Prescription Adherence by Medication Possession Ratio in Zagreb, Croatia

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Background: Poor adherence severely compromises the effectiveness of treatment, making this a critical issue in population health both from the perspective of quality of life and of health economics. Interventions aimed at improving adherence would provide a significant positive return on investment through primary prevention and secondary prevention of adverse health outcomes.

Objectives: The objective is to determine the adherence to chronic disease medication measured by MPR, and compare it with adherence that has been based on the patient's self-report from our previous study.

Methods:
Design: Observational study; pharmacy claims data analysis.
Setting: Pharmacy care; Zagreb, Croatia; October 2010–September 2011.
Exposures: Dates of medication fill/refill.
Main outcome measures: Medication Possession Ratio (MPR) and measured adherence as a function of the gaps between refills to provide timely information on the dynamics of patients medication adherence.
Statistical analysis: Descriptive statistics.

Results: According MPR, most patients were noncomplied (n = 96; 64.0%). Most patients (n = 130, 86.7%) were with one or more ATC group C (cardiovascular) medication prescribed. There is not a significant difference between group C medication and other medication according to adherence (p = 0.333). It needs to be noted that herein we present an analysis using overall MPR and C medication MPR, but the same analysis can be carried out on a drug class specific basis as well (using the drug class specific MPRs) if required. Medication nonadherence due to cost issues among study patients was evaluated.

Conclusions: The limitations of our study include several factors as: the consideration of a relatively small sample of patients, in case of medication switching adherence is difficult to measure with pharmacy claims data and some patients may have additional drug use not captured within the claims data. MPR does not provide accurate information on the continuity of medication usage and the precise measurement of each medication adherence, identification eventually drug stockpiles, measurement of gaps in medication supply with a special emphasis on allowable gap to obtain a refill of medicationis.

94. Therapeutic Inertia Research on Adult DM Patients in Taiwan

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Background: Mounting evidence has indicated that appropriate therapy for diabetes can prevent or delay the onset of complications. Goals for the management of diabetes (DM) are well defined, practical guidelines to deal with such complications have been widely disseminated. Despite these advances, health care practitioners often fail to adequately address these issues.

Objectives: This study evaluated therapeutic inertia and the failure of physicians to initiate or intensify therapy in response to the medical needs of diabetes patients, and linked these findings to the surrogate outcomes of glycemic control.

Methods: This study assembled a cohort of patients with diabetes. Data were obtained from the regular NHI claims database for the period from January 1, 2006 to December 31, 2008. Another database, a Pay-for-Performance (P4P) database, was used to supplement the regular claims data. Descriptive analysis and logistic regression models were used to assess therapeutic inertia in the care of DM patients and determine how it was influenced by patient, physician, and hospital characteristics.

Results: A total of 208,032 diabetic patients were included in the DM-P4P project, resulting in a total of 1,058,916 HbA_{1c} measurements. Approximately 32.3% of the subjects had HbA_{1c} test results exceeding 8%; in terms of therapeutic inertia, the physicians of these subjects failed to actively provide medication or treatment in approximately 55.7% of patient visits. Subjects with HbA_{1c} levels exceeding 8% were divided into two groups for comparison: those that had encountered therapeutic inertia and those that had not. Among the patients that encountered therapeutic inertia, 37.0% were treated by physicians with < 5 years of experience, and 32.5% were treated by physicians with more than 10 years of experience. Most of the participants in both groups received medical attention at hospitals in northern Taiwan and therapeutic inertia was most prevalent in primary care clinics.

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Conclusions: Fewer than one-half of patients with high HbA_{1c} levels had intensification of their medication. Interventions assisting physicians to regonize and overcome therapeutic inertia should improve diabetes care in the population.

95. Mining Medication Information from Clinical Discharge Summaries

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Background: In defining timeframe reference for clinical events and services in a specialized field, medical language processing (MLP) research deserves attention in pharmacovigilence.

Objectives: We developed a conceptual schema using Knowtator (v.1.5.2) to assess: (1) types of temporal information extracted to represent clinical concepts including medications; and (2) how accurately the open source MLP system, YTEX, extracts clinical concepts to answer temporal questions. The defined timeframe includes: pre-admission, hospital stay, and postdischarge.

Methods: The study processed de-identified 889 discharge summaries using YTEX to develop medical concept timeline structure. The result of the manual annotation was used to construct consensus consolidation of Knowtator to develop the gold standard for extraction performance analysis. Semantic types which classify the extracted concepts were determined based on MetaMap's predefined categories of medical concepts (e.g., Pharmacologic Substance, T121).

Results: It is observed that the section titles and the analysis within the identified sections increased the accuracy of time information. Analysis revealed that by default YTEX did not extract medication terminology. By configuring the dictionary look up table to include the semantic type, Pharmacological Substance, in the SNOMED library, medications were extracted with a precision, recall, and f-measure of 0.346, 0.388, and 0.366 respectively. To increase the recall, the medical glossary from National Cancer Institute (NCI) was added. Although the precision remained low (0.390), the recall nearly doubled (0.744), yielding an f-measure of 0.511. The temporal grouping of medications yielded the results: pre-admission ($p = 0.587$, $R = 0.692$, $F = 0.635$); Hospital Stay ($p = 0.133$, $R = 0.440$, $F = 0.204$); Post-Discharge ($p = 0.488$, $R = 0.727$, $F = 0.584$).

Conclusions: Knowtator can be used to manually annotate discharge summaries and other medical documents for fair establishment of a Gold Standard for clinical NLP. YTEX is a highly customizable extraction engine that allow for simple manipulation and complex extraction through table joining and manipulation.

96. A Review of the Use of Hospital-Based Databases in Observational Inpatient Studies of Drugs

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Background: The majority of pharmacoepidemiological studies employ data generated in primary healthcare. Regardless of the fact that prescription databases in hospital at an individual level have existed since the 1960s, few inpatient pharmacoepidemiological studies are available in the literature. The development and distribution of electronic medical record systems has made clinical and medical data more accessible for inpatient register-based research.

Objectives: This review describes hospital-based databases which have been used in inpatient observational pharmacoepidemiological studies, and it briefly provides an overview of research questions which have been addressed using these databases.

Methods: We applied simple chain searching and included databases in hospital settings containing data on inpatient drug use, which have been used for observational inpatient studies of drugs in following categories: (1) DRUG utilisation and prescribing practice, (2) studies of drug costs at individual level, (3) adverse drug effects and pharmacovigilance and (4) comparative effectiveness.

Results: Ten hospital-based databases in Asia, the US and Europe were found. One database covered hospital prescriptions for a well-defined source population, the remainder were single or multiple-sited hospital databases. Two databases were manually collected for research purposes, the remainder was automatically collected from claims data or generated from the clinical electronic medical records. The contents of the databases varied as well as possibilities of linkage with other data source like laboratory- and outpatient prescription data. Twenty studies were selected and discussed to illustrate the diversity of inpatient pharmacoepidemiological studies.

Conclusions: The number of pharmacoepidemiological inpatients studies is few compared with studies done in primary healthcare. Hospital-based databases have been used for drug utilization studies and studies of know adverse drug reactions either to confirm other studies or to describe the ability of the database to detect adverse drug reactions.

97. Early Access Programs: Resources for Pharmacoepidemiology Studies Prior to Product Approval

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Background: In recent years there has been a large increase in the demand for early access programs (EAP).

Reasons for this include: increased visibility of company pipeline products, innovative drugs for chronic or rare diseases are frequently sought before licensing, and demand for drugs in one country when awaiting approval in others. Yet very little is known about the scope of EAPs being conducted.

Objectives: This study aims to describe the frequency and characterizations of EAP that have been and/or currently being conducted.

Methods: The National Institute's of Health (NIH) database on Open Studies was utilized (www.clinicaltrials.gov) was analyzed for study and study population. Outcomes of interest include study initiation dates, regulation country, therapeutic areas, age range of participants and intervention types.

Results: A total number of 160 Expanded Access studies have been listed on the NIH database with 75 studies currently recruiting. Of these currently offering expanded access, 92% of studies were initiated in the last 5 years with the majority (72%) conducted under the US FDA, 11% in Asian countries (Taiwan, China, South Korea), a few in Canada, Europe, and Australia. Only three studies were conducted across country lines. For the study population, most programs recruited adults and both genders, although specific age groups and females were targeted. Only four studies specifically targeted only pediatric populations, but 26 studies recruited both pediatric and adult age groups. Interventions were mostly drugs (64%) but also included devices (17%), behavioral interventions (3%), and biological (3%), genetic (3%), and other (1%) products. More detail and time trends are available for a full presentation.

Conclusions: Early Access Programs are increasingly common, especially in the US, and include a wide variety of products and indications. They represent another potential resource whereby descriptions of patient populations not in clinical trials can be characterized prior to approval of a product.

98. The Humana Database – A Data Source for Pharmacoepidemiologic Research

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Background: Automated healthcare databases are frequently used for pharmacoepidemiologic research. The Humana database includes Humana member enrollment, medical, pharmacy, and laboratory data that can be readily accessed for study time periods beginning January 1, 2007. Investigators should be aware of the Humana database as a resource for pharmacoepidemiology research.

Objectives: To describe the Humana database, including its capabilities, strengths and limitations as they pertain to pharmacoepidemiologic research.

Methods: The data elements and capabilities of the Humana database were characterized. The database was queried to examine overall member characteristics.

Results: In 2011, the Humana membership totaled 11.2 million. The Medicare membership totaled 4.5 million, 1.9 million of which had a fully integrated medical and pharmacy Medicare Advantage Prescription Drug plan. The Commercial membership totaled 2.9, 1.6 million of which had fully integrated medical and pharmacy data. The remaining membership (3.8 million) was comprised of military, Medicaid and other types of coverage. Lab results are available for roughly 30% of patients; the percentage varies by disease state. A unique identifier provides reliable and direct linkage between the four administrative datasets. Members' healthcare utilization and outcomes can be evaluated longitudinally using all four datasets, and changes in enrollment information among members who move between insurance types can be tracked. The data provide information regarding mortality, detailed provider information, race/ethnicity and socio-economic status. The Humana database can serve as a source for recruiting members and providers for cross-sectional and prospective research (e.g., surveys, educational and behavioral interventions). The Humana claims data can be linked to several other Humana (e.g., behavioral economics, marketing and medical chart data) and non-Humana data sources (e.g., other claims datasets, national databases).

Conclusions: The Humana data represent a rich and valuable source of information for many areas of pharmacoepidemiologic research, including retrospective as well as prospective observational and experimental studies.

99. Utility of NCHS Public-Use Prescription Drug Files

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Background: The extent of reliable prescription drug utilization estimates within the NCHS surveys is unknown.

Objectives: Determine if NCHS surveys can produce reliable estimates of drug utilization.

Methods: Data from national multistage probability surveys NHANES-2007/2008 and NAMCS/NHAMCS 2008 were used in this study. The sampling unit for NHANES is at the person level and for the other surveys, the sampling unit is the medical visit. The number of evaluable generic (having ≥30 observations) and Multum Lexicon 2nd class-level drug mentions, were estimated overall and by specific subgroups (e.g., sex, age group, comorbidity, BMI, smoking, and insurance status). Estimates of mentions were produced for medications as a whole and the five most mentioned drugs/classes for each of the subgroups. Estimates based on < 30 observations or had a

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relative standard error > 30% were considered not evaluable.

Results: Overall, the percentages of evaluable drugs by survey were NHANES 16.3% (118/722 drugs), NHAMCS-ED 17.9% (149/834), NHAMCS-OPD 24.6% (308/1,253) and NAMCS 25.9% (295/1,141). The analysis of drug classes increased the evaluable percentages of NHANES to 50.0% (55/110), of NHAMCS-ED to 53.1% (69/130), of NAMCS to 57.4% (81/141) and of NHAMCS-OPD to 64.9% (100/154). Generally, the surveys produced acceptable estimates for prescription drugs as a whole, common drugs, and classes for each of the subgroups (e.g., sex, older age groups, race, and reported medical history). For the top five drugs, estimates were typically unreliable for younger age groups (0–14 and 15–24), subgroups based on diagnoses (NAMCS, NHAMCS-ED,NHAMCS-OPD), and the underweight subgroup (NHANES,NAMCS,NHAMCS-OPD).

Conclusions: The NCHS surveys provided evaluable estimates of drug utilization for a number of drugs and subgroups. In some subgroups defined by demographics or diseases, the survey sample also yielded evaluable estimation of drug use. Depending on the product or subgroup studied, combining surveys across several years may increase the reliability of drug utilization estimates. These surveys provide valuable data for nationally representative estimates of utilization of a number of drugs and drug classes on a population and utilization level.

100. Abstract withdrawn by author.

101. Development of Intervention Tools Demanded by the International Monetary Fund and the European Union To Improve Prescribing Quality of Acid Suppressive, Anti-platelet and Anti-Inflammatory Drugs

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Background: Portugal is in economic crisis due to overspending in many areas including drug prescribing. Thus, prescription rules based on international standards were demanded by September 2011 on a May 2011 memorandum of understanding for a 78 billion euro bailout loan to the country from a Troika of the International Monetary Fund, European Commission, European Central Bank.

Objectives: To swiftly develop rules as intervention tools to improve prescribing quality in three areas where patient safety and health system sustainability were being compromised: acid-suppressive, anti-platelet, and anti-inflammatory therapies.

Methods: This Portuguese team created the rules by adapting existing materials from an independent group of Harvard Medical School and Brigham and Women's Hospital Pharmacoepidemiology authors: iDiS. It produces educational outreach summaries backed by thorough reviews. First, materials were translated. Second, clinical practice differences were accounted for. Third, the strongest evidence was selected for the rules. Fourth, focus groups with family physicians provided input. Fifth, Portuguese Medical Association specialists were consulted.

Results: Focus groups suggested terminology and format modifications to increase acceptability. The Medical Association identified evidence gaps. These originated changes negotiated with original authors. The three sets of rules were issued by the Ministry of Health in September 2011 for public consultation.

Conclusions: The adaptation was extensively peer-reviewed, delivered on a tight timeline. Faced with time constraints and in crisis mode, adapting prescribing materials from recognized academic groups is a feasible alternative to creating rules afresh. Also, the rules outside origin made it easier to shield them from unduly local commercial influences. It is expected that pharmacoepidemiology will impact clinical practice: These rules have an estimated potential to save 12 million euro a year per set while improving patient safety, e.g., reduce Cox-2 inhibitors prescriptions in patients with previous cardiovascular events.

102. Contraceptives Use and Knowledge among Medical and Pharmacy Students

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Background: The early beginning of sexual activity and the inconsistent use of contraceptive methods are characteristics of young people sexuality which expose them to unplanned pregnancies and sexually transmitted infections. The correct knowledge and information on contraception is essential to change attitudes and therefore behaviors.

Objectives: The main objective of this study is to determine the prevalence of contraceptives use among medical and pharmacy students. We also want to characterize student's knowledge on contraceptives.

Methods: This was a cross-sectional study. Data were colected from a questionnaire filled by NOVA Medical School and ESTeSL-IPL students. All students, over 18 years old, were eligible for the study. Using a conve-

nience sampling method we collected 200 questionnaires, divided equally for both faculties. The primary measurement was the prevalence of contraceptives use at the time of the survey. Chi-square test was used for association between variables and independent t-test to compare groups.

Results: Of 152 of the 200 participants are sexually active. Almost 2/3 are women (71%) and the mean age was 20.8 ± 2.2 years old. The first sexual relation occurred before in pharm students (16.9 ± 1.6 year) compared to med students (17.6 ± 1.9 year) and when considering only 1st year students, this result has statistical significance ($p < 0.001$). 90.1% of the sexually active students used a contraceptive during their first sexual relation, mostly the male condom (80.5% pharm; 79% med). 80.9% claim to always use contraceptives. Male condom use is higher in med students and oral contraceptives in pharm students due to the higher proportion of males within the med students. The student's knowledge on contraceptives is generally adequate for most methods except for female condom (only 15.5%) and contraceptive implant (38.5%), with no difference between groups.

Conclusions: Although the use of contraceptives is very high in this population there are still almost 20% of sexually active students that don't always use a contraceptive during a sexual relation. Academic Health Institutions can play a decisive role in providing the information and knowledge required to behavioral change.

103. Clinical Pharmacy in General Practice in Central Denmark Region

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Background: Many patients in general practice (GP) are polypharmacy patients. Optimizing the medical treatment is a challenge to general practice.

Objectives:

Main objectives of the study: 1. develop a model for clinical pharmacy in GP; 2. test the utility of the model in daily practice; 3. evaluate the impact of the model used in the pilot project.

Methods: A randomised study on 20 GPs; 10 GPs in the intervention group and 10 GPs in the control group. In each practice medication reviews were made by a pharmacist for approximately 25 polypharmacy patients. The pharmacist was a regional medical consultant. In the medication reviews, focus were on indication, dosing, effect (treatment goal), interactions, side effects, local recommendations, technical issues. The primary outcome measure was the number of suggested interventions accepted by the GP, and the secondary outcome measure was the number of suggested interventions divided into subgroups.

Results: Medication reviews were made for 237 patients from intervention GP and 233 patients from control GP. For the 237 patients in intervention GP, there were found 636 suggestions to interventions for 214 patients, that is an average of three interventions per patient (0–10). Fifty-six percent of the suggested interventions were accepted by the GP. The 636 intervention suggestions were divided into five categories; change drug (207), discontinue drug (200), change dose (87), prescribe additional drug (59) and other (89). Reasons for intervention suggestions were divided into seven categories. The main reasons for intervention suggestions were effect/treatment goal, interactions/side effects and local recommendations/economy. The pharmacists found the making of medication reviews time consuming. GPs were positive towards the pharmacists, but suggested adjustment of the model for clinical pharmacy to fit into daily clinical practice.

Conclusions: Medication reviews by pharmacists resulted in an average of three intervention suggestions per polypharmacy patient. Fifty-six percent of these interventions were accepted by the GP. The model for clinical pharmacy in GP was time consuming and needs to be adjusted to daily practice.

104. Development and Validation of a Questionnaire to Assess Spanish-Speaking Patients' Knowledge about Their Oral Anticoagulant Treatment

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Background: Educational interventions addressed to patients under treatment with antagonists of vitamin K (VKA) anticoagulants are heterogeneous and lack patients' knowledge assessment. There are no validated instruments in Spanish to evaluate patients' knowledge about their anticoagulant medication.

Objectives: To develop and validate a questionnaire to assess Spanish speaking patients' knowledge about their oral anticoagulant medication.

Methods: The questionnaire had 35 questions or groups of questions, with 87 closed answers and 12 open answers. The instrument was reviewed by experts, hematologists and pharmacologists, for content validation.

Setting: Source population were patients under acenocoumarin or warfarin treatment, attending a thrombosis clinic at a second level hospital in Mexico City. Inclusion criteria: adult Spanish-speaking literate patients, who agreed to answer the questionnaire.

Exposures or interventions: Assessment of knowledge about anticoagulant medication in patients undergoing ac-

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enocoumarin or warfarin treatment. The questionnaire was answered in five different days by five subgroups of patients. Number of patients in five subgroups were: 28, 21, 17, 10, 10, total = 86.

Main outcome measures: Questionnaires were graded in two ways: (1) Overall correct answers, (2) correct answers minus wrong answers.

Statistical analysis: Descriptive statistics and variance analysis to test instrument reliability.

Results: Correct answer mean: 53.4, SD ±13.4 (range: 21–79); correct answer minus wrong answers mean : 39.5, SD ± 16.3 (range: -4 to 71). Analysis of variance showed no difference among different subgroups of patients tested on different days.

Time for answering the questionnaire: 20–45 minute age of patients: 24–87 years. Time on anticoagulant medication: 2 months–16 years.

Conclusions: This is a first effort to assess patients' knowledge about their anticoagulant medication through a validated instrument in Spanish. Results suggest opportunities for knowledge improvement through educational interventions addressed to patients undergoing oral anticoagulant treatment.

105. Health Care Screening and Preventive Practices in the United States Workforce

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Background: Current knowledge of screening and preventive measures among the US workforce remains incomplete.

Objectives: This study contributes to our knowledge of preventative care by examining current national estimates of flu and pneumonia shots, sidmoidoscopy or colonoscopy, mammograms and Pap tests among employed adults aged 20–64 years.

Methods: Cross-sectional observational study design. Analysis of nationally representative data collected from employed adults aged 20–64 years participating in the National Health Interview Surveys (NHIS) 2010 (total n = 13,844, men, n = 6,825, women, n = 7,019).

Results: An estimated 30.4% of the US workforce aged 20–64 years received a flu shot in the past year, 25% and 36.5% among working men and women, respectively ($p < 0.0001$). Employed men and women aged 50–64 years have similar rates of ever having received a pneumonia vaccine, 16.8% and 16.3%, respectively ($p = 0.7295$). The overall colonoscopy/sigmoidoscopy prevalence rate in the workforce (aged 50–64 years) is 55.4%, with rates of 54.9% and 56.0% among men and women, respectively ($p = 0.5899$). The overall rate among working women for having a Pap test within the past 3 years is 89%; Pap test rates are significantly different for women aged 20–39 years and aged 40–64 years (91.9% vs. 86.2%, respectively, $p < 0.0001$). An estimated 70.2% of employed women aged 40–64 years had a mammogram in the past 2 years.

Conclusions: Overall rates for flu shots and pneumonia vaccines are less than optimal in the US workforce, and men are less likely than women to avail themselves of a flu shot. Slightly more than half of appropriate aged men and women have had a colonoscopy or sigmoidoscopy. Effective approaches, including workplace education, are needed to improve upon these preventative care rates.

106. Adherence to Hospital Drug Formularies Varied in Denmark – A Comparison at the National Level

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Background: To avoid excessive cost of the drugs used, hospital drug formularies (HDFs) can be applied as a management tool to promote rational drug use. Little is known of the adherence to HDFs in secondary care, which is important to evaluate the use of drugs in or between the hospitals, at regional or national level.

Objectives: To evaluate the adherence to hospital drug formularies in Denmark.

Methods: Data on drugs used during 2010 were analyzed for 10 hospitals (two hospitals each from five regions), which constitute 30% of hospitals and 45% of hospital-beds in Denmark. Drug use data from individual hospitals were retrieved through the hospital pharmacies. Adherence to the HDF was analyzed at substance level using: drugs constituting 90% of the volume (=DU90%) and the adherence to the HDF in this segment (Index of Adherence). Data were analyzed at hospital level for all substances, and in addition for substances within ATC-code J01 and N02A. Substances with no DDD could not be included in DU90% analyses. However, they were included in the cost calculation.

Results: Substances used by hospitals varied between 791 and 1,093, and substances at HDFs varied between 155 and 528. Total drug utilization and cost varied between hospitals. University hospitals had higher use in DDD and cost per 100 bed-days. Index of adherence to HDFs varied from 43% to 91%. Within ATC-code J01 (antibiotics), DU90% varied between 12 and 19 substances, and index of adherence between 57% and 100%. Within ATC-code N02A (opioids), DU90% varied between three and five substances, and index of adherence between 51% and 100%.

Conclusions: The study detected a large variation in the number of substances at HDFs between hospitals. Low

adherence might reflect the low number of substances at the HDFs for the hospitals, specialist drugs were mostly not included at the HDFs. Adherence to antibiotics (J01) and opioids (N02A) was higher than adherence in general. Even though there has been a significant focus on using the least expensive opioid, there is still room for improvement.

107. Nurse-Led Interventions To Enhance Medication Adherence: Systematic Review and Meta-Analysis

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Background: Non-adherence to chronic medication remains a problem of striking magnitude with vast consequences and without solutions to date. Nurses are well positioned to provide adherence care, yet currently represent an underestimated and underutilized force in improving adherence and care outcomes.

Objectives: To synthesize evidence of the effect of nurse-led interventions on adherence to chronic medication.

Methods: Systematic review of randomised clinical trials on the effect of nurse-led interventions aiming to improve adherence to chronic medication. The search term medication adherence (MeSH-terms or synonyms) was combined with random* in PubMed and ISI Web of Knowledge to identify all relevant articles published in English from 2004 to 2009. The outcome, adherence had to be measured electronically with the Medication Event Monitoring System (MEMS®). Reference lists of retrieved articles were hand searched. Quality was assessed using the Cochrane risk of bias tool.

Results: Six studies met the inclusion criteria and were included. Their quality ranged from acceptable to good. Most nurse-led interventions were aimed at enhancing behaviour (adherence), knowledge and/or social support. In all but one studies the nurse-led interventions enhanced mean patient adherence significantly in the short term, varying from 5% to 22%. Of the four studies that reported adherence as a dichotomous variable (>90%), meta-analysis revealed an odd's ratio of 2.05 (95% CI 1.05–4.03), in favour of the groups that benefited from the nurse-led interventions. The effects in the long term were however inconsistent.

Conclusions: Nurse-led interventions can improve adherence to chronic medication but the effect is often of short duration. It seems tackling non-adherence demands continuous efforts and follow-up.

108. Adherence to Preventive Statin Therapy According to Socioeconomic Position

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Background: Statins are increasingly prescribed to prevent cardiovascular disease (CVD) in asymptomatic subjects (i.e., without established CVD or diabetes). Yet, adherence to the life-long preventive therapy is a challenge – potentially more so in subjects of lower socioeconomic position (SEP).

Objectives: To investigate the influence of SEP on long-term statin adherence among incident asymptomatic statin users.

Methods: Population based cohort study (2002–2009), applying data from Danish nationwide registries with individual-level information on demographics, dispensed prescription drugs and hospital discharges. Within a cohort of all Danish adult residents we indentified subjects without previous register markers of CVD or diabetes who redeemed the first statin prescription during 2002–2005 – with or without drug markers for primary/essential hypertension (HT). Incident statin users were followed for 4 years or until a censoring event (death, emigration, register markers of any type of CVD or diabetes). SEP indicators were quintiles of disposable family income and highest attained education (four levels).

Statistical methods: Proportion of days covered (PDC) with tablets during the observation period was calculated, using adherence to therapy corresponding to PDC ≥80% as main outcome measure. Logistic regression analyses were applied to estimate Odds Ratio (OR) with 95% confidence interval (CI) for statin adherence within the observation period, applying a SEP indicator as determinant, including as confounders HT and age in 5-years age groups.

Results: Among subjects aged 40–64, adherence increased for each increase in income quintile by 12%, OR 1.12, CI (1.10–1.14) in men and 4%, 1.04 (1.02–1.06) in women. For education the figures were 1.04 (1.01–1.07) and 0.97 (0.94–0.99), respectively. Among subjects aged 65+, the ORs were 1.07 (1.03–1.11) and 1.00 (0.98–1.03), applying income as SEP-indicator. For education the figures were 1.03 (0.98–1.08) and 0.97 (0.93–1.00), respectively.

Conclusions: Individuals in lower SEP are less likely to follow long-term preventive statin therapy. This holds especially for men and when income is applied as SEP-indicator.

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109. Healthcare Resource Utilization (HRU) Associated with Hospitalization for Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) and Subsequent Post-Hospitalization Recurrence and Death: A Danish Cohort Study

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Background: Up to 25% of AECOPD events require hospitalizations. However, there are limited data on HRU associated with the AECOPD hospitalization and on subsequent post-discharge recurrence and mortality.

Objectives: To characterize HRU associated with AECOPD hospitalizations and examine risk of recurrence and mortality within 30 and 180 days after discharge from an AECOPD hospitalization.

Methods: We conducted a population-based cohort study of prevalent COPD patients in Northern Denmark with at least one AECOPD hospitalization between 2005 and 2009. We identified all AECOPD hospitalizations and described median length of stay (LOS); proportions admitted to the intensive care unit (ICU), treated with non-invasive ventilation (NIV) or mechanical ventilation (MV) during the admission; and in-hospital mortality. We also examined risk of recurrence and death within 30 and 180 days after being discharged alive from an AECOPD hospitalization. Recurrence was defined as use of prescriptions for both antibiotics and oral corticosteroids (OCS) on the same day or readmission, as markers for moderate and severe AECOPD, respectively.

Results: We identified 3,176 COPD patients. Median age was 72 years, 55% were female. Of the 6,612 AECOPD hospitalizations in this cohort, the median LOS was 6 days, 8.6% included ICU admission, 2.9% had MV use, and 7.2% had NIV use. In-hospital mortality was 5.6%. The median duration from first to second AECOPD hospitalization was 53 days (IQR 19–127). Within 30 days post-discharge of the 6,240 admissions in which patients were discharged alive, 5.7% filled prescriptions for antibiotics and OCS, 13.3% were readmitted to hospital, and 4.2% died. Within 180 days after discharge, 19.9% filled prescriptions for antibiotics and OCS, 34.7% were readmitted to the hospital, 2.9% were treated with MV, and 17.4% died.

Conclusions: AECOPD hospitalizations are serious events with considerable HRU and risk of post-discharge recurrence and death, representing a substantial healthcare burden.

110. A Proposed Checklist to Interpret Cross-National Comparison Studies of Drug Utilization

Elena Ballarin,[1] Pili Ferrer,[2] Mònica Sabaté,[1] Hans Petri,[3] Marietta Rottenkolber,[4] Joan Fortuny,[5] Joerg Hasford,[4] Luisa Ibáñez.[1] *[1]Pharmacology-Universitat Autònoma Barcelona, Foundation Catalan Institute of Pharmacology, Barcelona, Spain; [2]Foundation Catalan Institute of Pharmacology, Barcelona, Spain; [3]Roche Products Limited (Pharmaceuticals), Welwyn Garden City, United Kingdom; [4]Institut für Med. Informationsverarbeitung, Biometrie und Epidemiologie, Ludwig-Maximilians Universität, Mucnich, Germany; [5]Novartis Pharma, Barcelona, Spain.*

Background: Few publications exist reporting the validity of national drug consumption databases (NDCDB). Other aspects may influence the interpretation of patterns of drug use (DU) across countries.

Objectives: To develop a checklist of factors affecting cross-country differences in DU and to test it for antiepileptic drugs (AED) in Denmark (DK), Norway (NO) and Catalonia (CAT).

Methods: The following list of items were assessed to explain differences in AED use in DK, NO, and CAT: (1) validation studies and data quality checks for each NDCDB; (2) tabulate AED use, preferably with ATC/DDD methods; (3) quantify inter-country variation by a coefficient of variation; (4) drug data source; (5) population coverage; (6) healthcare setting definition; (7) drug information (e.g., dose, days of supply); (8) demographic characteristics; (9) prevalence of conditions treated by the drugs: selection of the main indication for use based on the DDD assignment; (10) clinical guidelines; (11) national health policy. Data was retrieved from the Danish Prescription Register (DanPR), the Norwegian Prescription Database (NorPD) and the DATAMART database (CatDB) for the outpatient sector.

Results: NDCDB internal checks information, and sensitivity and specificity studies were available for DanPR and NorPD, but not for CatDB. The population coverage rate for DanPR, NorPD and CatDB was 100%, 100% and 70%, respectively. Information on dispensed, prescribed and reimbursed medicines was available for DK, NO and CAT. None database recorded indication for use. Variability in DDD/1,000 inhabitants/day (DID) was seen mainly at ATC level 5 (e.g., in 2009, consumption of lamotrigine was 0.77 (CAT), 3.07 (NO) and 3.28 (DK) DID). Disparate population characteristics between DK/NO and CAT. Epilepsy prevalence is 3.6/1,000 persons in NO and 7.7/1,000 in DK, no data for CAT. No differences found in clinical guidelines. Reimbursement and advertising policies were more restrictive in DK and NO.

Conclusions: This structured checklist provides an analytical approach to cross-national comparison studies of DU.

Even if information on indication for use had been available, this checklist would explain DU differences across countries.

111. Inpatient Drug Consumption in Europe (PROTECT Project)

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Background: Figures reflecting the drug utilization (DU) resulting from inpatient healthcare settings at a national level are scarce, even though drugs prescribed in hospitals impact outpatient prescription patterns and total drug expenditures. National inpatient databases could be a basic tool for cross-national comparisons (CNCs).

Objectives: To review the availability of national inpatient DU data. To report the number of inpatient DU studies published since 1980 for drugs selected by PROTECT.

Methods: As a part of the PROTECT inventory on drug consumption databases, information on the type of drug use data and the covered healthcare sector was assessed for 11 European countries (http://www.imi-protect.eu/results.html). In addition, a PubMed search was conducted, with the following keywords: "hospital drug consumption" AND each of the medicines group (i.e., calcium channel blockers, benzodiazepines, antidepressants, antiepileptics, and β2-adrenergics). Antibacterials were excluded as their use has been comprehensively studied. Inclusion criteria were: studies on patterns of drug use regardless of indication, located in any type of European hospital, and published since 1980.

Results: Denmark, Sweden, Norway and France receive information on inpatient DU at a national level from wholesalers/manufacturers. IMS Health is the provider in England. In Italy, drugs dispensed to patients in hospitals are reimbursed by the regional health authorities and, thus, registered. Only for Denmark data is freely available online. Finland, Spain, Germany, Netherlands and Poland do not have inpatient DU information. One hundred and sixty-four out of the 797 abstracts retrieved from PubMed and reviewed were included, but none for β2-adrenergics. Only 15 studies used the ATC/DDD methodology recommended by the WHO and one single study compared inpatient DU at a national level between two countries.

Conclusions: There are no national administrative structures that enable monitoring inpatient DU. Studies on inpatient patterns of drug use are scarce. Several factors may hinder the monitoring of inpatient DU and the conduct of CNCs including definition of inpatient healthcare, information on hospital activity, or application of ATC/DDD methodology.

112. Are Health Authorities and Health insurance Companies Taking Full Advantage of the Availability of Generic Risperidone; Implications for the Future?

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Background: Multiple demand side initiatives have been introduced across Europe to enhance prescribing of generics in a class or related classes with varying degrees of success depending on the nature and intensity of the reforms. These include initiatives to enhance prescribing of generic anti-depressants (ADs) vs. patented ADs, as well as generic PPIs, statins and ACEIs vs. ARBs. However, limited initiatives to enhance the prescribing of generic atypical anti-psychotics (AAPs) apart from prescribing restrictions for injectable risperidone and olanzapine in some countries.

Objectives: Analyse the influence of general demand side measures to enhance utilisation of generic (oral immediate release risperidone) vs. patented AAPs.

Methods: (1) Typically quasi-experimental study using a segmented time series design of monthly AAP utilisation and expenditure in 2011 DDDs (ATC N05AH03–06, N05AL05, N05AX08, 11–13); alternatively yearly analyses up to 2 years before generic risperidone available and reimbursed up to 6 years after in Austria, Belgium, Ireland (GMS population), Scotland, Spain (Catalonia), and Sweden; (2) Pertinent demand side measures recorded. Only administrative databases used.

Results: Preliminary analyses show reduced utilisation of risperidone in Austria, Scotland and Spain (Catalonia) as a % of total AAP utilisation over time following the availability of oral generic risperidone; with stable utilisation in Ireland and the UK (NHS Bury) as a % total AAP utilisation.

Conclusions: Full analyses are currently being conducted to further explore the influence of different demand side measures across Europe to enhance the prescribing of gen-

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eric risperidone. However, preliminary results suggests there is no cross transfer of general initiatives enhancing the prescribing of generics first line or first switch to increase prescribing efficiency, i.e., generic oral risperidone vs. patented AAPs. Consequently, specific measures may be needed to enhance prescribing of generic oral risperidone especially as the disease area is more complex than conditions requiring a PPI, statin or ACEIs. This will be explored further to give future guidance.

113. Essential To Review Health Policy Initiatives When Comparing Utilisation Patterns across Countries?

Brian Godman,[1] Marion Bennie,[2] Stephen Campbell,[3] Kristina Garuoliene,[4] Marija Kalaba,[5] Vanda Markovic-Pekovic,[6] Vera Vlahovic-Palcevski,[7] Bjorn Wettermark,[8] Corrine Zara,[9] Lars L Gustafsson.[1] *[1]Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden; [2]Strathclyde Institute for Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, United Kingdom; [3]Primary Care Research Group, University of Manchester, Manchester, United Kingdom; [4]Medicines Reimbursement Department, National Health Insurance Fund, Vilnius, Lithuania; [5]Republic Institute for Health Insurance, Belgrade, Serbia; [6]Faculty of Medicine, University of Banja Luka, Banja Luka, Bosnia and Herzegowina, Republic Srpska,; [7]Unit for Clinical Pharmacology, University Hospital Rijeka, Rijeka, Croatia; [8]Centre for Pharmacoepidemiology, Karolinska University Hospital Solna, Stockholm, Sweden; [9]Barcelona Health Region, Catalan Health Service, Barcelona, Spain.*

Background: Previous research has highlighted differences in utilisation of products across Europe. However, limited explanations.

Objectives: Assess utilisation of PPIs, statins and ACEIs/ARBs across Europe alongside health policy initiatives.

Methods: Retrospective observational study of ambulatory care patients in up to 20 European countries and regions dispensed any PPI (A02BC), statin (C10AA) or ACEI/ARB between 2001 and 2010. Utilisation in 2010 DDDs and DDDs/TIDs; only administrative databases. Demand side measures recorded.

Results: Increased utilisation of PPIs, statins and ACEIs/ARBs across all countries, e.g., typically between two and over fivefold for statins and 70% to 160% for ACEIs/ARBs (2007 vs. 2001). However can be considerable differences in rates (DDDs/TID). PPIs (2007/2008): 1.8 Republic of Sprska, 2.28 Lithuania, 3.1 Serbia and 13.4 Croatia to 36.7 Sweden, 76.9 Scotland and 82.8 Catalonia (Spain) – Lithuania 2.81 (2009), 5.96 Srpska (2010) to 100.2 Scotland (2010). Statins (2007): 0.8 Lithuania, 3.28 Serbia, 5.0 Republic of Srpska, 28.5 Croatia to 49 Catalonia (Spain), 53.5 Sweden, and 116.8 Scotland 1.82 Lithuania (2009), 8.79 Srpska (2010) to 142.82 in Scotland (2012). ACEIs/ARBs (2007): 61.6 Republic Srpska, 104.3 Croatia, 116.8 Sweden, 130.1 Lithuania, 149.3 Serbia, 152.9 Catalonia (Spain), 165.2 Scotland and 191.8 Portugal. Reasons for low utilisation PPIs and statins include high patient co-payments and prescribing restrictions, e.g., statins restricted to secondary prevention in Lithuania (initially also only for 6 months), Republic of Srpska and Croatia (primary prevention in Croatia for persistent high levels). High utilisation of statins in UK helped by quality targets linked with financial incentives combined with studies encouraging higher strength statins. Typically limited restrictions for ACEIs/ARBs and hypertension seen as a serious diseases reduces variation in practice.

Conclusions: Some substantial differences in utilisation patterns (also seen for antihistamines) make it essential where possible to record potential reasons behind any differences seen. Otherwise, may be tendencies for readers to dismiss the outliers.

114. Opportunities To Enhance Prescribing Efficiency for Patients with Diabetes in Abu Dhabi without Compromising Care

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Background: Previous studies have shown considerable opportunities to enhance prescribing efficiency in Abu Dhabi with the PPIs and statins. There may also be opportunities to improve prescribing efficiency for patients with diabetes, which is a growing public health problem.

Objectives: Analyse current treatment approaches among patients with T2DM and compare these with international standards. Secondly, assess the extent of different management approaches among different facilities to direct future initiatives to improve prescribing efficiency.

Methods: Audit of 561 random T2DM patients' records across three facilities, with patients' medication history checked for available data over a 6 month period. This included extent of patient monitoring (BP, lipids, HbA_{1c}, etc.), oral glycaemic drugs prescribed, whether prescribed at maximal doses before insulins, whether insulin treatment delayed and insulin type, and extent of high cost medications prescribed, e.g., higher cost extended release formulations and patent protected products vs. multiple source standards.

Results: Different prescribing patterns across facilities. However, appreciable utilisation of MR vs. standard oral drugs across facilities. Approximately 47% of patients on gliptins, 20% of patients prescribed Sitagliptin 50 mg twice daily instead of 100 mg once daily, and up to 23% of patients on newer long acting insulins (Glargine and Detemir) with generally limited use of older insulins. Variable HbA_{1c} measurement – with $HbA_{1c} > 10\%$ in 14% of

patients and only 48% of patients with controlled HbA_{1c}. Greater number of patients on three or more oral drugs in specialist centres. Costs could be reduced by approximately 30% through following international guidelines and reducing utilisation of expensive MR preparations and newer insulins. Care could also be improved by regular monitoring of HbA_{1c} levels.

Conclusions: Potential to appreciably improve quality and efficiency of care of T2DM patients in Abu Dhabi mirroring PPIs and statins. Introduction of Pharmacy Benefit Management Systems should improve step wise care and reduce utilisation of expensive MR and patented preparations without compromising care.

115. Influence of Recent Initiatives in the Republic of Srpska to Improve Prescribing Efficiency; Influence and Future Direction

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Background: Pharmaceutical spending in Republic of Srpska (1.433 mn) increased from Euro28/capita (2005) to Euro75/capita in 2010. Multiple reforms include a basic list of drugs (List A – with up to 10% co-payment) and supplementary List B (not first line/more expensive – 50% co-payment), compulsory price cuts, reference pricing for generics, formularies and prescribing restrictions.

Objectives: Assess the influence of measures to increase prescribing efficiency of PPIs, statins, and ACEIs/ARBs 2003 to 2010. Classes chosen as high volume and contain generics, originators and patented products, with all products essentially similar.

Methods: Retrospective observational study of ambulatory care patients in Republic of Srpska health insurance database dispensed at least one reimbursed prescription for any PPI (A02BC), statin (C10AA), ACEI/ARB (C09AA, C09BA,C09CA/C09DA). Utilisation in 2011 DDDs and DDDs/TID. Reimbursed expenditure as health insurance perspective. Demand side measures recorded.

Results: (1) PPIs – List B since May 2008 with no prescribing restrictions (only restrictions on some doses). 3.3-fold increase in utilisation 2008 to 2010 (5.96 DDD/TID in 2010) driven in part by increasing lanzoprazole and esomeprazole. Reducing expenditure/DDDs for most PPIs limited increase in expenditure to just over threefold driven by greater use more expensive PPIs; (2) Statins relisted 2004 (List B from May 2008) and only secondary prevention including DM. Utilisation increased over 19-fold 2010 vs. 2004 (8.79 DDD/TID in 2010) but expenditure only 4.1-fold due to decreasing expenditure/DDDs (3) ACEIs/ARBs listed with 50% co-payment with no restrictions. Utilisation increased from 27.37 DDD/TID in 2003 to 171.16 in 2010 (6.3-fold). Decreasing expenditure/DDDs for ACEIs limited increase in expenditure to sevenfold despite increasing use of FDCs at premium prices.

Conclusions: Reforms have reduced expenditure/DDD for products over time helping to moderate expenditure despite growing volumes. Further reforms required for PPIs and ACEI FDCs to take full advantage of decreasing expenditure/DDDs.

116. Comparing and Contrasting Reforms To Improve Prescribing Efficiency for Different Drug Classes in Croatia

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Background: Multiple reforms have reduced expenditure in Croatia and increased the number of new reimbursed innovative molecules. Measures include reference pricing (ATC 3–5), education, financial incentives and restrictions. Prescribing restrictions for ARBs limited their expenditure despite a 87% increase in utilisation (2010 DDDs) 2007 vs. 2001. Parkinson disease (PD) is the second most common neurological disease affecting the elderly. Consequently, should be a focus of "payer" scrutiny with increasing use of premium price add-on therapies to stabilise or improve motor function.

Objectives: Assess whether ongoing reforms have increased the prescribing efficiency in PD in recent years – efficiency defined is increasing use of newer add-on therapies for similar expenditure.

Methods: Observational retrospective study of the Croatian Institute for Health Insurance (HZZO) database of drugs used to treat patients with PD in Croatia (ATC N04BA to BX) from 2000 to 2010 in DDDs (2010 DDDs). Narrative review of recent reforms in Croatia to increase prescribing efficiency, and their influence, from internal sources or published papers.

Results: Utilisation of PD drugs increased by 218% during the study period driven by increasing use of add-on therapies, i.e., entacapone, pramipexole, and ropinirole, along with increasing use of levodopa. Reimbursed expenditure increased by 360% (2010 vs. 2000) driven by increased use of patented add-on therapies. However, supply side reforms decreased overall reimbursed expendi-

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ture/DDD in 2010 vs. 2004, including -20% for ropinirole, -35% for levodopa, and -53% for entacapone. As a result, reimbursed expenditure moderated in recent years despite growing utilisation.

Conclusions: PD is a complex treatment area with expenditure driven by the need for add-on therapies to improve care. However, reforms have stabilised expenditure on PD drugs in recent years despite increasing volumes enhancing prescribing efficiency, mirroring PPIs, statins and ACEIs/ARBs. Expenditure on PD drugs should start falling as more add-on therapies lose their patent, negating the need for additional measures.

117. Are Targeted Initiatives Needed to Enhance Prescribing Efficiency: Scotland as a Case History

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Background: Multiple demand and supply side measures for the PPIs, statins and ACEIs vs. ARBs have appreciably enhanced prescibing efficiency. PPI expenditure fell by 56% 2010 vs. 2001 despite threefold increase in utilisation (DDDs) with statin expenditure increasing only 7% during this period despite 6.2-fold volume increase; ACEI/ARB expenditure stable 2001–2007 despite 159% increase in volume (DDDs).

Objectives: Analyse whether general demand side measures have enhanced the prescribing of generic losartan (first reimbursed July 2010) vs. patented ARBs and/or generic risperidone (first reimbursed April 2008) vs. patented atypical anti-psychotics.

Methods: (1) Quasi-experimental study using a segmented time series analyses of monthly ARB utilisation (NHS Scotland Data Warehouse) in DDDs (C09CA01–09; C09DA01–04, 06–08; C09DB01, 02, 04, 05; C09DX01–03) July 2008 to September 2011; monthly atypicals in DDDs (N05AH03–06, N05AL05, N05AX08, 11–13); (2) retrospective analysis of utilisation (DDDs) and reimbursed expenditure of atypical antipsychotics 2005–2010; (3) Demand side measures recorded.

Results: (1) Preliminary analysis shows stable utilisation of generic losartan: 32% to 34% total ARBs 2 years before generics to 1 year after; (2) Atypical utilisation increasing 50% 2010 vs. 2005 although risperidone decreasing from 21% of total atypicals (DDD basis) in 2005 to 16% in 2010, with newer atypicals (quetiapine, aripiprazole and paliperidone) increasing (17.5% to 32%); (3) Atypical expenditure increasing by 42% (Euro4950 in 2005 to Euro7039 in 2010); moderated by 84% reduction in expenditure/DDD for oral generic risperidone in 2010 vs. pre-patent loss prices; (4) No specific additional demand side measures directing prescribing of losartan (as other ARBs shortly available as generics) or generic risperidone until recently where prescribing targets for oral vs. patented dispersible risperidone (engineering).

Conclusions: No apparent cross transfer of general initiatives encouraging prescribing of generics in a class. Consequently, specific measures needed to enhance prescribing of losartan or oral risperidone to appreciably increase prescribing efficiency. ARB prescribing efficiency will be enhanced with more patent loses.

118. Approaches to Enhance Prescribing Efficiency in France; Influence and Future Direction

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Background: Multiple demand side measures enhanced prescribing of generics vs. originators in France. However for PPIs and statins, utilisation of patented products increased whilst multiple sourced products decreased following generics. P4P measures (CAPI) including financial incentives for increased prescribing of generic PPIs, statins, antidepressants (ADs) and ACEIs (usually generics) vs. ARBs introduced to change this. Generic losartan reimbursed in France (March 2010) with generic modified release (MR) venlafaxine in November 2008. Generic immediate release mirtazapine since 2005; although other formulations patent protected. No specific campaigns directing prescribing of losartan, venlafaxine and mirtazepine although generic venlafaxine and mirtazapine included in AD targets.

Objectives: (1) Analyse the influence of demand side measures on utilisation of losartan vs. patented ARBs; (2) similarly generic mirtazapine and venlafaxine vs. patented ADs.

Methods: (1) Time series analyses of monthly ARB utilisation (C09CA, C09DA, DB, and DX) in 2011 DDDs among Echantillon Généraliste de Bénéficiaires (permanent 1/97 sample of health insurance beneficiaries) January 2009 to June 2011; (2) Observational study of utilisation of newer anti-depressants – ADs – (N06AX11, 16, 21, and 22. N06AX18 and 23 not reimbursed in France); (3) Narrative review of demand side measures.

Results: Initial results show (1) limited change in utilisation pattern if losartan pre- and post- generic availability; greater change with other single ARBs although limited change when combined; (2) utilisation of generic mirtazapine stable at 83% to 89% total mirtazepine; (3) generic utilisation (venlafaxine and IR mirtazapine) decreased

from 82% of total selected antidepressants in January 2009 to 70% in June 2011 (DDD basis). However, utilisation stable at 70–72% in past year.

Conclusions: Stabilisation of losartan, mirtazapine and venlafaxine utilisation (past year) different from PPIs and statins post generics (2001–2007) where saw reduced utilisation of generic PPIs and statins. Additional targeted measures should enhance prescribing efficiency, with efficiency of ARBs improving with generic candersartan (January 2012).

119. Evaluating 1 Year Production of the Collaborative Centre of the Brazilian Unified Health System (SUS): A Partnership between Academy and Government for Improving Pharmaceutical Assistance

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Background: Pharmaceutical asistance is divided in Basic, Strategic, and Specialized Components. The last one is responsible to provide appropriate treatment for high-cost diseases. Treatments are provided and paid by the government. With approximately 19 mi people and a crescent ageing population in an ever growing new-drugs scenario, Minas Gerais State Health Authority is facing new demands in a context of restricted budget. This result in the necessity of adopting procedures for prioritizing and evaluating what might be delivered for citizens.

Objectives: Evaluate results for the public health system of the partnership between academy and government for health technology assessment.

Methods: Medicines incorporation demands come from industry but also from non-government organizations and prosecutors for diseases sometimes already treated with government founding. State Committee for Pharmaceuticals Selection evaluates demands and whenever necessary requests the Collaborative Centre (CCSUS) for independent appraisal. Committee also requests comparative effectiveness studies to evaluate performance of medicines incorporated. Studies are done by means of patients follow-up for treatment outcomes evaluations, linkage of administrative and health databases and by literature reviews. The production of the CCSUS for the Health Authority in the 12 months period has been revised aiming to describe and estimate its relevance for Society.

Results: CCSUS is an independent organization with credibility in society and Government. More than thousands of specialized medicines demands have been analyzed in compliance with Brazilian Protocols. Systematic reviews towards incorporation and disincorporation and technical appraisals have also been conducted supporting judicial and administrative decisions.

Conclusions: CCSUS is providing stakeholders with fast and decisive information. The partnership between Academy and Government seems to be helpful for improving pharmaceutical assistance in a context of restricted health budget with a rising number of lawsuits involving Health Authority.

120. Gender and Drug Utilization – A Systematic Analysis of Gender Differences in Incidence of Drug Therapy in Sweden

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Background: Gender differences in drug utilization have been demonstrated in several therapeutic areas. However, there is a lack of comprehensive overviews on gender differences in entire populations, and particularly on the incidence of drug treatment.

Objectives: To systematically describe and analyse gender differences in incidence of drug treatment in the Swedish population.

Methods: A retrospective cross-sectional study with data from the Swedish Prescribed Drug register, including all drugs dispensed to the Swedish population (9 million inhabitants). All ATC 2nd level groups with ambulatory care prescribing accounting for >75% of the total volume in DDDs and a prevalence of >1% were included. Gender differences were analysed for different pharmacological groups in 2010. Incident use was defined as initial dispensing of a pharmacological group after a wash-out period of 365 days. Incidence was measured in age adjusted number of patients per 1,000 person-years (pat/1,000 PYs) and differences between the sexes were calculated in both absolute and relative values (with 95 CI).

Results: Fifty pharmacological groups were included in the study. Groups with large gender difference in absolute values with higher incidence in women were antibiotics (154 vs. 127 pat/1,000 PYs), drugs for acid related disorders (37 vs. 27 pat/1,000 PYs) and anxiolytics (28 vs. 19 pat/1,000 PYs). Groups with higher incidence in men were vasodilators (6 vs. 9 pat/1,000 PYs), lipid modifying

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agents (11 vs. 14 pat/1,000 PYs) and ACE inhibitors (12 vs. 15 pat/1,000 PYs). Large relative differences with higher incidence in women were seen for antimycotics (RR = 5.5 [5.4–5.6]), thyroid therapy (RR = 3.5 [3.4–3.6]) and drugs for treatment of bone diseases (RR = 3.5 [3.4–3.6]). Large relative differences with higher incidence in men were seen for antigout preparations (RR = 0.44 [0.42–0.45]), psychostimulants (RR = 0.70 [0.68–0.72]) and antidiabetics (RR = 0.73 [0.72–0.75]).

Conclusions: There are differences in drug utilization between men and women in Sweden. Differences in incidence or prevalence of disease may explain some of the observed differences while other differences are difficult to explain based on medical grounds.

121. Drug Utilisation Study in a Public Hospital Southwest Nigeria – A Retrospective and Prospective Study

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Background: Rational drug use (RDU) is a crucial part of the National health policy, particularly since more than 50% of national and 60–80% of individual health care spending in Nigeria goes towards medicines.

Objectives: To assess rational drug use and patients' knowledge of medicines prescribed in a typical Nigerian public hospital.

Methods: A cross- sectional study involving retrospective analysis of prescriptions of patients that visited the outpatient pharmacy unit of the State General Hospital, Ilaro, Ogun state from January 2009 to December 2009 followed by a 2 month prospective analysis and patient interview.

Main outcome measures: WHO/INRUD prescribing indicators and patient care indicators for rational drug use.

Statistical analysis: Statistical analysis on the results was performed using the Statistical Package for the Social Sciences (SPSS), version 16.

Results: For the retrospective study, a total of 720 prescriptions (3,426 medicines) were analysed, and for the prospective study, 120 patients were interviewed with a total of 664 medicines prescribed. Average number of medicines per prescription was 4.76 ± 1.6, medicines prescribed by their generic names was 23.3% (n = 798). Furthermore, 98.4% (n = 3,370) of the drugs prescribed were from the Nigerian EDL and 42.5% (n = 306) and 35.8% (n = 258) encounters resulted in the prescription of an antibiotic and an injection respectively. Average drug cost per encounter was N1, 033.21k. (USD6.5). The average consultation time was 4 ± 1.79 minutes in 67 (56%) out of the 120 patients prospectively studied and 7 ± 2.30 minutes in 53 (44%) patients. The dispensing time in all the 120 patients ranged from 3 to 7 minute. Of the prescribed drugs, 89.9% (n = 597) were supplied but none of the drug envelopes had the patient's name on it. Confirmation of drug instructions during patient – dispenser encounters was done in only 43.3% (n = 52) of the patients while 68.3% (n = 82) of the patients interviewed knew the correct dosage of their drugs.

Conclusions: There is a need for a mix of interventions to curb the irrational prescribing of medicines and to improve dispensing practices in the hospital.

122. Time and Motion Studies Alongside Clinical Trials: Scientific and Operational Considerations

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Background: Time and Motion (T and M) studies are designed to collect observational data to quantify efficiency-related outcomes, mainly staff time and consumables associated with medical interventions, with the aim to understand resource use burden (total care time and cost).

Objectives: Identify and describe key scientific and operational considerations related to the design and implementation of T and M studies conducted alongside multinational clinical trials.

Methods: Using a case study approach, common design features, and analytical and operational considerations associated with this methodology have been summarized.

Results: T and M endpoints are to be carefully selected to cover as many of the relevant and observable elements of the treatment and patient care process as possible, while remaining simple and straightforward for study observers to document. Given clinical trial context, T and M study results may not wholly reflect real-world care and outcomes, but pre-study process of care mapping through structured staff interview and/or direct observations of care process at selected sites remain essential to inform both protocol and CRF design. An early evaluation of the expected number of trial patients in sites participating in T and M and trial subject recruitment schedules are critical to plan adequate T and M sample sizes and data collection period duration. In the absence of clear guidelines on T and M study classification, regulatory processes need to be better understood. As T and M study methodology is relatively uncommon for study sites, streamlined communications and focused, site-based training is crucial.

Conclusions: T and M studies enable the collection of valuable efficiency-related outcomes in support of the commercialization and launch of medicines and medical devices. T and M is a flexible methodology that is well suited for application alongside clinical trials. Early identification of methodological and operational challenges is crucial to ensure a scientifically robust design and operational feasibility.

123. Analysis of the Relationship between the Antibiotic Consumption and the Bacterial Resistance in a Private Hospital of Mexico City

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Background: In spite of high rates of bacterial resistance in Mexico, the available information on the levels of use of antibiotics and their relationship with the bacterial susceptibility in hospitals is scarce.

Objectives: The main goal of this work is to analyze the relationship between the consumption of antibacterial drugs and the bacterial susceptibility.

Methods: A descriptive study of consumption. The data are dispensations of antibacterial drugs in the hospital pharmacy from 2006 to 2010. Drugs are presented in the classification Anatomical Therapeutic Chemical and the consumptions in Defined Daily Doses (DDD). Data of microbial susceptibility and consumption of antibacterial drugs during the year 2010 were analyzed simultaneously using the indicator "Drugs Utilization (DU 90%)."

Results: The 5 year period consumption varied between 69 and 80 DDD/100 beds-days DDD. The number of used drugs ranged from 49 to 52 and the number of these within the segment DU 90% ranged between 15 and 18. The most consumed groups were "Other B-Lactams cephalosporins (J01D)," which increased their consumption from 14 to 19 DDD/100 DDD beds-days from 2006 to 2010. They were followed by the "quinolones (J01M)," with values between 16 and 22 DDD/100 beds-days, and by "Carbapenems (J01D3)" which an increase of 3–5 DDD. The general susceptibility showed a 39% of resistance. In more than half of the 32 drugs included in the test of susceptibility resistance values $>40\%$ were observed, and the first three drugs positioned in the segment DU 90% (ceftriaxone, ciprofloxacin and levofloxacin) showed resistances between 50 and 60%. From 17 drugs of the DU 90% six are not included in the tests of microbial susceptibility.

Conclusions: The increase of antibacterial drugs during the year 2010 it is not justifiable with hospital statistics, which show a tendency to decline. The pattern of general susceptibility shows high rates of resistance in a large number of common use antibiotics. There is a lack of susceptibility in a significant number of the most used drugs, favoring their irrational use. The analysis of consumption associated with the microbial susceptibility within the DU 90% was an effective tool for the detection of problems associated with the consumption of antibacterial drugs.

124. Use of Brand Names of Discontinued Brand Drug Products by Prescribers When Generic Equivalents Exist

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Background: Prescribing of brand names following discontinuation of brand drug products has not been formally documented in published literature. Regulators and industry are therefore unclear about the actual potential for drug name confusion medication errors for newly developed brand names when conflicts are identified with a brand name of a discontinued brand drug product.

Objectives: To describe the use of brand names in prescribing after discontinuation of brand drug products to inform the formulation and evaluation of new brand names.

Methods: A national outpatient prescription database, IMS's Vector One®: National, was used to examine drug use data for seven solid oral dosage form brand drugs that were discontinued but generic versions were still marketed. Data for brand names *as they were written* on actual prescriptions were evaluated from 2003 to 2010.

Results: Data showed the continued use of brand names by prescribers for all seven drugs. The brand name "Aldomet" was written on 8% of prescriptions for methyldopa in the year 2010; Atarax for hydroxyzine, 34%; Luvox for fluvoxamine, 23%; Micronase for glyburide, 5%; Relafen for nabumetone, 19%; Serzone for nefazodone, 8%; and Toradol for ketorolac, 37%. The number of prescriptions written for the brand name for all drugs decreased over time but did not cease following brand drug discontinuation. Use of the brand name Aldomet decreased by 17% over the 7 year period; and Atarax by 39%, Luvox by 22%, Micronase by 2%, Relafen by 63%, Serzone by 80% and Toradol by 49% since brand drug discontinuation. Of the seven drugs, "Aldomet" showed the longest continued use; approximately eight out of 100 new prescriptions were still written in the brand name 10 years after brand drug discontinuation.

Conclusions: Prescribers continued to use the brand names of discontinued brand drug products long after discontinuation. This suggests that there is a potential for confusion between the brand name of discontinued brand drug product and the newly developed brand name when orthographic or phonetic similarity exists. Therefore, the brand names of discontinued brand drug products need to be considered when formulating and evaluating new brand names.

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125. Risk of Herb-Drug Interactions Associated with the Consumption of Psychoactive Substances among Health Technologies Students

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Background: The concurrent use of herbs and/or nutritional supplements with psychoactive effect and prescription medications is common among college students. Herbs, vitamins, and other dietary supplements may influence the effects of prescription and nonprescription drugs leading to adverse consequences, by increasing the potential for interactions.

Objectives: The main objective of this study was to evaluate the risk of herb-drug interactions associated to the consumption of substances with psychoactive effects in Health Technologies students.

Methods: A convenience sample of 180 students, stratified by academic year and degree course, was surveyed to determine the prevalence of psychoactive substances consumption using self-filling questionnaires. The primary outcome was the prevalence of prescription and OTC medications, herbal products and dietary suplements consumption. Potential interactions were identified from a literature search of documented interactions. Chi-square test and Spearman correlation coefficient were used to evaluate the association between variables, with a significance level of 5%.

Results: Participants age distribution varied between 18 and 25 years old. Xanthines and alcohol consumption were mentioned by 97% of students, herbs/dietary supplements with stimulant effect by 61%. The consumption of anxiolytic drugs and calming supplements, at least once in the previous 12 months, was identified in 56% of students. Moderate correlations were found between concomitant use of anxiolytic prescription drugs and herbal preparations/dietary supplements with relaxing properties ($p = 0.568$) with a potential risk of synergistic effects and in anxiolytic prescription drugs and dietary supplements with stimulant effect ($p = 0.502$), with a potential risk for antagonistic effects.

Conclusions: These findings suggest that a considerable percentage of participants is at risk for a potential herb-drug interaction. This future health professionals must recognise the consequences of these substances consumption and use reliable resources to assess the safety of these products with regard to modify the potential risk for interactions.

126. Abstract withdrawn by author.

127. Attitudes, Perceptions and Knowledge of General Practitioners towards Adverse Drug Reaction Reporting in Malaysia: Preliminary Results

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Background: The main form of pharmacovigilance system in Malaysia is the spontaneous voluntary reporting system for adverse drug reaction (ADR) set up by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC). Although this system has been in place for over 10 years, it has been plagued by low reporting rates. Statistics showed that general practitioners (GPs) in Malaysia contributed $< 5\%$ of the reports although this trend is reversed in developed countries.

Objectives: This study aims to determine the practice, knowledge, attitude and perception of GPs in Malaysia towards ADR reporting, as well as to investigate the reason(s) for non-reporting.

Methods: This is a cross-sectional questionnaire-based survey among private GPs who are practicing in Kuala Lumpur, the capital city of Malaysia. Purposive non-random sampling was employed. A total of 21 out 41 GPs, whose clinics are within a 4-km area in the city centre, participated in the pilot study. Data were collected using a self-administered questionnaire in a face-to-face setting.

Results: The majority of the pilot study subjects were males (81%), clinic-owners (61.9%) and have practiced medicine for over 30 years (47.6%). None of them reported to MADRAC for the past 1 year, albeit 19.0% of them had done ADR reporting at least once in their practice. The majority of the GPs (61.9%) have medium level of knowledge about ADR reporting with 71.4% were not aware of the ADR reporting scheme. The two most common reasons that influenced non-reporting were the lack of information on how to report ADRs (52.4%) and the difficulty to decide whether an ADR has occurred due to the lack of clinical knowledge (38.1%). Most of them agreed that ADR reporting should be made compulsory (57.1%), but the majority also want the reporting system to hide the identity of the prescriber (52.4%).

Conclusions: The zero ADR reporting rate for the past 1 year among GPs in the pilot study is alarming as this may reflect the findings of the actual study. Additional GPs are currently being recruited to further strengthen any suggestions to improve the low reporting rate.

128. Retrospective Multinational Chart Review Studies of Adverse and Serious Adverse Events in Europe: Opportunities and Challenges

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Background: Retrospective adverse and serious adverse event (AE/SAE) data are useful inputs to epidemiological, safety, benefit-risk, and health economic studies designed to support product commercialization and launch. These data are not typically available from health care databases but, if reported by physicians, can be obtained from patient medical charts to estimate event rate incidence, clinical outcomes associated with poor drug tolerability, and total costs of care.

Objectives: To identify scientific and operational challenges in relation to the collection of drug safety outcomes through retrospective chart review studies.

Methods: A critical review and qualitative analysis of five recent European multinational chart review studies designed to inform health economic, clinical outcome and/or safety questions was performed to delineate main methodological and operational challenges associated with the abstraction, analysis, and reporting of AEs/SAEs.

Results: Chart review studies of safety outcomes can provide data not otherwise available from most secondary healthcare data sources. However, unless explicitly documented in the chart, causal relationship between AEs/SAEs and medications cannot be assumed. Resource utilization attributable to particular AEs/SAEs may be incomplete/not easily discernible, separate and apart from the underlying disease/comorbidities. Directives for regulatory reporting of retrospective safety data and whether waivers of expedited reporting can be obtained is unclear. Reporting of AEs/SAEs in chart reviews varies markedly depending on sponsor standard operating procedures (SOPs), as SOPs typically lack explicit guidance on this matter.

Conclusions: Despite significant challenges, practical, and scientifically sound approaches to the design and conduct of multinational chart review studies that prioritize the collection of AEs/SAEs are possible. Main scientific and operational challenges need to be identified early during the design phase. Unambiguous guidance from regulatory authorities with respect to reporting of retrospective safety data is warranted.

129. Risk Factors for Acute Decompensation of Chronic Kidney Disease in Hospitalised Patients in Nephrology Department

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Background: Although baseline renal insufficiency is known to be a risk factor for acute renal failure (ARF), few studies actually quantified the association between the level of preexisting kidney function and subsequent risk of ARF.

Objectives: To investigate risk factors of ARF in patients with chronic kidney disease (CKD), a case-control study was conducted in Nephrology department at Sfax hospital between 1st November 2010 and 31 July 2011.

Methods: All patients with baseline renal insufficiency hospitalized for acute renal failure were considered as cases. They were compared with control patients with CKD. A conditional logistic regression model was used to identify independent risk factors for ARF in patients with CKD.

Results: A total of 57 cases were compared with 112 control subjects. In multivariable models, hypertension, diabetes, all heart diseases, and exposure to non-steroidal anti-inflammatory drugs were independent risk factors for ARF in patients with chronic kidney disease. However, exposure to calcium channel blockers has a protective effect against the risk of ARF on CKD (OR = 0.25; IC 95%: 0.08–0.83).

Conclusions: Concerted efforts to prevent or intervene early may reduce the high risk of progressive CKD and death documented after ARF.

130. Effectiveness of Actions to Improve the Adherence of Pharmacological Treatment, in Diabetic and Hypertensive Patients: Experience of Mexico

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Background: Lack of treatment adherence is a health serious problem; it has been reported that this occurs in 50% to 65% of patients.

Objectives: To evaluate the effectiveness of incorporating a pharmacist to the primary care health team to increase the proportion of diabetic and/or hypertensive patients with adherence to pharmacological treatment.

Methods: This report evaluates a "pharmacotherapy intervention" provided by pharmacists through an experi-

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mental design that included two family medicine units (FMU) of the Mexican Social Security Institute (IMSS). Patients with diagnosis of diabetes and hypertension were included. The FMU of intervention (FMUi) started a service that was called "counseling," provided by pharmacists; in the FMU control (FMUc) the patients received a leaflet with information about antidiabetic and antihypertensive drugs. The main outcome variable was the increase in the proportion of patients with adherence to the pharmacologic treatment. The change of medication adherence was measured through pill count. A baseline and three subsequent measurements were carried out during the follow-up (6 months). Chi-square was used to compare the proportions of patient's adherence between two units.

Results: Of 160 patients were included in the FMUi and 229 in the FMUc, the mean age were 58 ± 10 and 62 ± 10 years old in each FMU. In both clinics the proportion of females was higher. Thirty percent of the patients in the FMUi had diabetes type II (DM2), 35% had essential hypertension (HT) and 35% had DM2 and HT; in the FMUc these percentages were similar (27%, 34% vs. 39%). At baseline, the lack adherence was 28%; the two main reasons were drugs were not dispensed at the pharmacy and forget to take them. After the intervention the percentage of patients which adhere to pharmacological treatment by pill count increase in both studied units (72.5% to 82% and 72% to 87%; $p < 0.05$, respectively).

Conclusions: In both FMU, the proportion of patients that had adherence increased, these suggest that it is important implement any of these actions to promote the adherence to drug treatment in patients with chronic diseases.

131. Psychosocial Factors Associated with the Prescription of Generic Drugs by Dentist in Morocco

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Background: The Generic medicines prescription (GMP) in Morocco progress but still controversial.

Objectives: The aim of our study is to evaluate factors associated with GMP behavior in Morocco using the ASE (Attitude, Social Influence and Self-Efficacy) Model.

Methods: Dentists were sent a validated and anonymous questionnaire measuring the ASE and Motivation variables for GMP and their generic drug prescription percentage. The mean scores and the 95% confidence intervals (95% CI) were calculated. A binary logistic regression was used to identify the variables that best predict GMP behaviour.

Results: Most (n = 146; 53.8%) responded to this cross-sectional survey. The mean age was 35.9 years old. Le sex-ratio male/female = 0.68. 47.9% dentists practicing in the public sector and 47.2% in private practice. The main advantages and incentives for generic prescribing were "saving money" and "follow the recommendations of limitations." The greatest influence was social "health insurance." The prescription of generic resource represented 50–75% of the average total prescription. ASE and the items have motivations were the best predictors: they explain 53% of generic prescribing. The perceived behavioral control influence high prescription (OR = 2.312), p = 0.013, and IC95% (1.197–4.465].

Conclusions: GMP percentage is very low among dentist compared with other doctors. Interventions to modify the Attitudes towards generic medicines should be implemented.

132. Abstract withdrawn by author.

133. Management of Neurogenic Detrusor Overactivity in Patients with Spinal Cord Injury in Taiwan

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Background: Neurogenic detrusor overactivity (NDO) presents a great disease burden on patients with spinal cord injury (SCI). However, literatures reporting medical and demographic characteristics of NDO complications in SCI patients remained limited.

Objectives: To investigate current management pattern of NDO in SCI patients.

Methods: Data containing 2 million randomly sampled individuals from the National Health Insurance Research Database (NHIRD) in Taiwan were used to conduct a cross-sectional study. Patients with emergency department visits or hospitalizations for SCI defined by ICD-9 codes 806.X and 952.X between 2006 and 2008 were retrieved. The frequency of NDO complications in SCI patients was evaluated by three approaches: (1) diagnosis codes defined by ICD-9 codes 596.5 and 788.3 (excluding 596.53); (2) patients receiving pharmacological treatments for urinary incontinence e.g., alpha blockers, antimuscarinic agents, and cholinergic agents; and (3) patients receiving urinary catheterizations defined by NHI codes 47013C and

47014C. We assessed patient demographics, concomitant medications, comorbid conditions, and NDO treatment options.

Results: Of 941 eligible individuals were identified from 2006 to 2008, of which 165 (17.5%) were NDO cases with a mean age of 54 and consisting of 64% male. Most NDO patients received alpha blockers (33%), followed by antimuscarinic agents (26%) and cholinergic agents (15%). Sixty-seven percent of NDO patients received urinary catheterizations.

Conclusions: While various pharmacological treatment options are available to treat NDO, many SCI patients have resolved to use urinary catheterizations, indicating that more effective treatment options may be needed to further improve patient care in the future.

134. Factors Associated with Prescription and Nonprescription Drug among Children Living in Poor Areas

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Background: This high consumption of prescription and non-prescription medications incurs risks to children's health. It is, therefore, important to investigate factors associated with the use of medications.

Objectives: To examine the factors that influence utilization of prescription and non-prescription drugs in the pediatric population, in Brazil.

Methods: A population-based, household sample survey was carried out between February and May 2006 in which children living in selected households in representative micro-regions of the city of Salvador were evaluated. The use of prescribed and non-prescribed medication in the 15 days preceding the interview was considered the dependent variable. Adjusted analysis was performed using multinomial logistic regression following a hierarchical model.

Results: Of the 1,382 children, 18.7%, the mother reported that the child had taken prescribed medication and 29.3% the child had taken medication that had not been prescribed by a physician. Following adjustment for confounding variables, the following factors were found to be positively associated with the use of prescribed medication: age (4–5 and 6 years of age), mother's perception of her child's health as poor/very poor, presence of chronic disease, interruption of activities due to health-related problems, number of medical consultations, having consulted a doctor irrespective of whether the child was ill or not, and reported expenditure with medication. A negative association was found between the use of non-prescribed medication and mothers of African descent, while a positive association was found with age (4–5 years), being female, mother's age (30–39 years), mother's perception of the child's health as poor/very poor, interruption of activities due to health-related problems and reported expenditure with medication.

Conclusions: These results point to a need for programs to optimize access and rationalize the use of medication in children in Brazil.

135. Differences in Gastroprotective Medication Use between Australia and Nova Scotia, Canada

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Background: Histamine H2 antagonists (H2RAs) have long been used for peptic ulcer disease and reflux. Proton pump inhibitors (PPIs), more recently introduced, are many-fold more expensive, especially compared to generic H2RAs. As price and incremental cost-effectiveness are higher than alternatives and inappropriate use is well documented, there was concern about rapidly rising public expenditure for PPI subsidy. PPIs are more effective in preventing upper GI bleeds but long term PPI use is associated with increased fracture risk (confirmed by recent meta-analyses) and infections.

Objectives: The aim was to compare use of H2RAs and PPIs (gastroprotective agents), during the 5 year period 2001–2005, in elderly and social security beneficiaries in two jurisdictions (Australia [AUS] and Nova Scotia, Canada [NS]).

Methods: Dispensing data were collected for H2RAs and PPIs. In AUS, dispensing data for concession beneficiaries were obtained from Pharmaceutical Benefits Scheme database. In NS these were sourced from Pharmacare database. Relevant populations were used to convert to Defined Daily Doses per 1,000 beneficiaries per day (DDD/1,000/day).

Results: Overall use of gastroprotective agents rose in a similar way in NS to AUS (100–160 DDD/1,000/day) during this 5 year time window. However, the proportion of this use accounted for by PPIs was far higher in AUS (up to 85%) than in NS (23% rising to 35%). In AUS PPI use rose from 50 up to about 140 DDD/1,000/day, whereas in NS this rose slowly to be almost 60 DDD/1,000/day in 2005. H2RA use in NS was high (over 100 DDD/1,000/day) whereas in AUS H2RA use fell from 54 to around 24 DDD/1,000/day over this period.

Conclusions: AUS had much higher use of PPIs than NS over the time period 2001–2005, probably due to differ-

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ences in adherence to reimbursement criteria. These utilisation variations could lead to differences in current health outcomes from resultant adverse effects of PPIs. More fractures, or increased use of antiresorptive agents, in AUS could be apparent. Comparison of DXA scans in the two jurisdictions, or of population T-scores could be interesting ways of exploring any resultant effects of the higher utilisation of PPIs in AUS.

136. Racial and Ethnic Differences in the Use of Prescription and Nonprescription among Children Living in Poor Areas

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Background: Access to drugs and their benefits are distributed unevenly between the various layers of society and the various racial groups.

Objectives: To analyze the consumption of medicines and major therapeutic groups for children according to skin color, living in Salvador, Bahia, Brazil.

Methods: We conducted a population-based household survey in the period from February to May 2006, which studied 1,382 children aged between 4 to11 years of age, 138 white and 1.244 black, from households selected in micro-representative areas of Salvador. The dependent variable was the use of medications in the last 15 days preceding the interview. We considered three groups of explanatory variables: socioeconomic, health status indicators and use of health services.

Results: Of 1.382 children, according to the mothers, 663 (48%) were using some kind of medication, 267 (19.3%) took prescription drugs and 396 (28.7%) non-prescription medicines. The percentage of drug use, according to skin color, was: 54.3% of white women and 47.3% among black women. Regarding the use of prescription drugs, 19.6% and 18.6% in white and black children, respectively, and 34.8% and 28.7% for non-prescription medicines. Among children of black skin color most consumed pharmacological groups were analgesics (14.2%), systemic antibiotics (3.6%), antitussives (3.2%), anti-asthmatics (2.3%) and anti-helmintic (2.2%). White children used more analgesics (19.6%), systemic antibiotics (5.8%), antitussives (5.1%), antihistamines (5.1%), anti-asthmatics (4.3%) and anti-helmintic (2.2%). After multivariate analysis the determinants of greater drug use among black children were: age (4–5 years), female gender, worse self-rated health of children by the mother, business interruption due to health problems and health care regardless being sick, both in the last 15 days.

Conclusions: Among the possible causes of racial inequalities in the use of drugs, there are the socioeconomic differences that accumulate throughout life of successive generations. It is suggested that racial discrimination and its impact on health, is at the origin of these inequalities.

137. Patterns of Use of Antimuscarinic Drugs for Overactive Bladder: A Study of the Norwegian Prescription Database

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Background: The effect of drug treatment for overactive bladder (OAB) can be limited if patients have low adherence and persistence to medications.

Objectives: To investigate the epidemiology of use of antimuscarinic drugs for OAB in Norway, including adherence and persistence of use.

Methods: Observational study.

Sample: Data from the Norwegian Prescription Database during the years 2004–2010.

Main outcome measures: Adherence was measured as medication possession ratio (MPR). Switching was defined as any change from the index medication to one of the other four study drugs.

Statistical analysis: When studying new users, only patients not taking any OAB drug during the first 24 months of the observational period were included. MPR was calculated as the sum of days of supply for all packages purchased except the last filling, divided by the total number of days from the first date of purchase to the last date.

Results: In 2010, 0.94% of the population in Norway had filled at least one prescription for an anticholinergic drug for OAB; a gradual increase from 0.75% in 2004. In females the frequency was 1.30%; in males 0.59%. The use was highest in the age group 80–89 years, with 4.6% (5.2% in females, 3.6% in males).

Among new female users (n = 42,329) the first drug filled was solifenacin for 42.5%, tolterodine for 33.4%, darifenacin for 12.4%, fesoterodin for 8.2% and oxybutynin for 3.5%. After 1 year, the percentage still purchasing the same drug was 21.3% (23.3% for solifenacin, 22.4% for tolterodine, 20.8% for darifenacin, 12.4% for fesoterodin and 10.8% for oxybutynin). Mean MPRs among new users were 0.68 for fesoterodin, 0.67 for darifenacin, 0.62 for solifenacin and 0.60 for tolterodine. The proportions with MPR >80% were 38.5% for fesoterodin, 36.6% for darifenacin, 35.5% for solifenacin and 33.7% for tolterodine.

The overall switch rate among new users was 17.4%(35.0% for oxybutynin, 22.4% for tolterodine, 17.6% for darifenacin, 13.6% for solifenacin and 9.7% for fesoterodin.

Conclusions: Among new users of antimuscarinic drugs for OAB, only 21.3% still purchased the same drug after 1 year, and the switch rate was 17.4%.

138. Vascular Protection with ACE Inhibitors or Angiotensin II Receptor Antagonists Following Type 2 Diabetes Treatment Initiation in Elderly

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Background: Canadian practice guidelines recommend that ACE inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) be used for vascular protection in people with diabetes at high risk of cardiovascular event including diabetics aged ≥65.

Objectives: To estimate the proportion of elderly who initiated either an ACEI or an ARB (ACEI/ARB) in the year following the beginning of an oral antidiabetes drug (OAD) treatment and to identify factors associated with this initiation.

Methods: Using the Quebec Health Insurance Board databases, we conducted a population-based cohort study of individuals aged ≥65 who were newly dispensed an OAD between 2000-01-01 and 2008-12-31 and had no claims for an ACEI/ARB in the preceding year. Factors associated with ACEI/ARB initiation were identified using multivariate logistic regression.

Results: Among the 43,700 study individuals, 13,621 (31.2%) initiated an ACEI/ARB in the year following OAD initiation. Individuals were more likely to initiate an ACEI/ARB if they initially received both metformin and a sulfonylurea, lived in a rural region, initiated their OAD between 2001 and 2006, were hospitalized or made >22 medical visits in the year preceding OAD initiation. Individuals aged ≥75, those who were prescribed an OAD by a general practitioner, initially received a sulfonylurea or received ≥4 different medications in the year preceding OAD initiation, were less likely to initiate an ACEI/ARB.

Conclusions: In the elderly not already taking ACEI/ARB, a low proportion of those undertaking an OAD treatment are initiated in the following year to the recommended cardio-protection of ACEI/ARB. Interventions are needed to close this gap.

139. Treatment with Rivastigmine or Galantamine and Risk of Hospitalization for an Adverse Cardiac Event: A Database Study from the Netherlands

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Background: Two Cholinesterase inhibitors (ChEIs), rivastigmine and galantamine, are used to treat Alzheimer Disease (AD) in the Netherlands. Some adverse cardiac events have been reported for these medications.

Objectives: The present study assessed whether the use of ChEIs increased the risk of hospitalizations for adverse cardiac events in the Netherlands.

Methods: A cohort-crossover study of the Dutch PHARMO Record Linking System database included patients who initiated ChEIs at age 50 or older, had at least one ChEI dispensing between 1998 and 2008, 1 year history in PHARMO-RLS prior to ChEI initiation and one subsequent dispensing of any medication. The outcome was a first hospitalization for syncope, AV block, heart failure (HF), dysrhythmia, ischemic heart disease (IHD) or myocardial infarction (MI). Poisson and Cox regression with time-dependant exposure variates were used to calculate incidence densities (ID) and hazard ratios (HR) for adverse cardiac events during periods with ChEI use, as compared to periods without ChEI use.

Results: During the mean observation period of 8.9 years (Interquartile range: 6.7; 10.2) there were 569 cardiac events among 3,358 patients. The adjusted IDs were significantly increased during ChEI exposure for syncope, AV-block, HF and MI, when compared to the background ID in the roughly 5 years prior to the last year before ChEI initiation. However, when exposed periods were compared to the unexposed periods of 1 year before ChEI initiation and times after exposure, the adjusted HRs were not significantly increased for syncope, AV-block, HF, dysrhythmia or MI. The adjusted HR for IHD was 1.91 (95% CI: 1.00–3.67).

Conclusions: Exposure to ChEIs might increase the risk of adverse cardiac events, but the small numbers of cases limit conclusions about the risk in this population.

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140. Cardiovascular Disease Prevention among US Nursing Home Residents with Diabetes

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Background: Cardiovascular disease (CVD) is a major contributor to morbidity and mortality for persons with diabetes. Type 2 diabetes is associated with an increased risk of macrovascular disease, and comorbid hypertension and dyslipidemia are also risk factors for this disease. Guidelines recommend use of statins and ACE Inhibitors (ACEI) or ARB's to prevent cardiovascular events among diabetics.

Objectives: To describe adherence to guidelines for CVD prevention in US nursing homes (NH).

Methods: We performed a large nationally representative cross-sectional study using the 2004 National NH Survey. Within the sample of NH diabetics, we identified three groups of people with: (1) hypertension; (2) CVD or 1+ risk factors of CVD; or (3) neither. Within each of these groups, we evaluated cardiovascular medication utilization patterns, including use of statins and ACEIs/ARBs. We conducted bivariate analyses to characterize the prevalence of use of these agents both overall and by age and gender.

Results: Overall, 43.3% of diabetics took an ACEI or ARB. Use of an ACEI/ARB was more prevalent (51.2%) in diabetics with hypertension than in those without hypertension (29.7%). From age 65 to 85, use of ACEI/ARB increased (51.3–54.3%), while use decreased after age 85 (46.0%). There was no difference in the prevalence of ACEI/ARB by gender. The pattern for use of statins was similar. Overall, 23.5% of diabetics treated with statins. Use of statins was higher in high risk residents (25.3–27.3%) and increased until age 75 and then decreased thereafter. Approximately 30% of residents age 65–74 received statins, while 25.4% of patients aged 75–84 and 13.6% of those over the age of 85 used statins. Men were more likely to be treated with statins than women (26.7% vs. 22.1%).

Conclusions: Use of cardiovascular medications was low in a NH population with diabetes and comorbid hypertension or CVD. For both ACEI/ARB and statins, use was more common in relatively younger adults, but decreased after age 85 for ACEI/ARB and age 75 for statins. While guideline adherence was suboptimal, these data may reflect the reality that limited data exists about the risk to benefit ratio of using these medications in older NH residents.

141. Patterns of Drug Use by Initiators of Dabigatran and Warfarin: Uptake and Persistence

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Background: Dabigatran (DBG), a novel anticoagulant for use in non-valvular atrial fibrillation (AF), was approved by FDA in October 2010. Prior to this, warfarin (W) was the only oral anticoagulant option for clinicians for decades. Adverse events have been reported post marketing and further active surveillance activities are planned.

Objectives: To compare patterns of initiation and use of DBG and W among elderly US Medicare patients, focusing on uptake and persistence behaviors, with the goal of informing protocol development for assessing post-market safety issues.

Methods: Patients were enrolled in new-user DBG or W cohorts provided that at their first eligible prescription, they were age ≥65, were not in a nursing home, and during the preceding 183 days, were enrolled in Medicare Parts A, B and D, had a diagnosis of AF, had no dispensings of DBG or W, and had no diagnoses of: deep vein thrombosis, pulmonary embolism, joint replacement, rheumatic mitral valve, valve repair, or prosthetic heart valve.

Results: Presently available data showed 30,266 DBG and 137,337 W initiators from October 2010 through December 2011. Monthly initiators of DBG increased through March 2011 and then leveled off at an average of 2,684 initiators per month from March through October 2011, while an average of 9,259 patients initiated W monthly during the same period. Days supplied were <30 days in 3% DBG and 17% W users; 30–59 days (nearly all for 30 days) in 87% DBG and 60% W users; and >90 days in 10% DBG and 21% W users. Persistency of use beyond 30 days was 64% in DBG vs. Seventy-five percent in W initiators; beyond 60 days, it was 54% in DBG and 61% in W initiators.

Conclusions: In Medicare elderly with non-valvular AF, the initiation of DBG was approximately 29% that of W from March to October 2011. DBG initiators were more likely to have 30–59 days supplied than W users; and W initiators were more likely to have short (<30 days) or long (>90 days) days supplied than DBG initiators. DBG initiators had less persistence than W initiators. Data will be updated as available, demographics and

switching behavior added, and additional exclusions considered.

142. Characteristics of Elderly Patients Prescribed Sitagliptin and Other Oral Antihyperglycemic Agents in a Large U.S. Medicare Claims Database

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Background: Observational studies comparing drugs can be biased due to differences in baseline demographic and clinical characteristics of patients initiating new therapy.

Objectives: Characteristics of elderly Medicare Advantage Plan (Humana) patients with type 2 diabetes mellitus (T2DM) initiating sitagliptin were compared to elderly patients initiating other oral antihyperglycaemic agents (OAHA).

Methods: Patients aged ≥65 with T2DM (N = 85,479), at least 1 year of continuous enrollment, and initiating at least one OAHA prescription between 2008 and 2010 in the HUMANA Medicare Advantage Plan were studied. Treatment included mono, dual, and triple/other therapy. Specific diabetes related complications reported withint 12 months prior to treatment were defined.

Results: Compared to elderly patients treated with other OHA, elderly sitagliptin patients were more likely to be Caucasian (82.3% vs. 75%, $p < 0.0001$), were equally likely to be male (49.5% vs. 47%, $p < 0.0001$), older (66.8% ≥70 years of age vs. 67.9%, $p < 0.0001$), and were mostly receiving sitagliptin in triple/other therapy (72.4%). Prevalence of diabetes complications were either similar or lower for sitagliptin patients compared to those treated with other regimens (Retinopathy: 11.5% vs. 18.7%, $p < 0.0001$; Neuropathies: 14.8% vs. 23.1%, $p < 0.0001$; Proteinuria: 3.8% vs. 4.4%, $p < 0.0001$; Renal failure: 9.9% vs. 14.8%, $p < 0.0001$). These observations were confirmed in a multivariate logistic regression model simultaneously including all of the baseline characteristics studied.

Conclusions: A trend, previously found in patients <65, for sitagliptin to be prescribed to sicker, younger patients, is not evident in this elderly population, potentially due to a survival effect or other factors driving prescribing patterns in the elderly. Differences in baseline characteristics need to be considered in pharmacoepidemiology observational study analyses to try to control for potential biases.

143. Use of Vitamin K Antagonists in Friuli Venezia Giulia, Italy, 2001 to 2010: A Population-Based Study

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Background: Vitamin K antagonists (VKAs) are often prescribed in elderly patients. Due to the narrow therapeutic index and the risk of adverse hemorrhagic events, management of VKA therapy requires particular care, especially in elderly due to comorbidities and the potential of interactions with comedications.

Objectives: To describe the pattern of VKAs use according to age in the population of Friuli Venezia Giulia (FVG), Italy, approximately 1.2 million, from 2001 to 2010.

Methods: This population-based study used the FVG Outpatient Prescription Database to identify all residents prescribed VKAs, by ATC code B01AA, during 2001–2010. Residence in FVG was defined through record linkage with the Patients Identification Database. Annual and age- specific prevalence was calculated.

Results: A total of 61,051 residents, 50.9% men, were dispensed VKAs, receiving 994,435 prescriptions (average 16.3 prescriptions per user). From 2001 to 2010 the annual number of users increased by 38.7% from 16,258 to 26,543. A parallel increase in the number of prescriptions by 52%, from 60,988 to 126,932, was found. The prevalence of use in 2001 was 1.4%, 1.3% in women and 1.4% in men, and increased to 2.1%, 2.0% in women and 2.3% in men, in 2010. The prevalence was 1.5% below age 50 and increased with each age category, up to a peak of 12.9% from age 70 to 79. In subjects 80 years or older, the prevalence was 10.6%. At the first prescription of VKAs, 37% of subjects were in the age category 70–79. Overall 23.8% initiated VKAs at the age of 80 years or older, in women this percentage increases to 31.6%.

Conclusions: Frequent monitoring of anticoagulation during therapy initiation and maintenance is recommended in all patients and particularly in elderly. Women are reported to require lower doses to maintain a therapeutic range than men of the same age. In our population the prevalence of VKAs use increased with age and a high proportion of users, in particular women, start therapy in old age.

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144. Variation in the Days Supply Field for Osteoporosis Medications in Ontario

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Background: Pharmacy claims data are commonly used to examine patterns of drug utilization and to classify drug exposure in postmarketing research. However, the accuracy of the days supply field has not received great attention.

Objectives: To describe the days supply reported for osteoporosis drug classes (bisphosphonates, calcitonin, raloxifene) by dosing regimen and examine if the days supply reported matched the typically expected dosing interval.

Methods: We used data submitted to the Ontario Drug Benefits program (ages 65+ years) to examine the variation in days supply reported for osteoporosis medications, 1997–2011. The number and proportion of days supply values submitted were summarized by dosing regimen (daily-, weekly-, and monthly-oral; nasal spray; cyclical – 14 days active drug +76 days calcium; and yearly infusion), and residence status (community or long-term care [LTC] resident). We defined "typically expected" days supply by the dosing regimen: daily in 7-, 30- or 100-day intervals, weekly in 7- or 30-day intervals, monthly and nasal spray in 28- or 30-day intervals, and cyclical as 90-day supply.

Results: We identified 17,615,404 osteoporosis prescriptions dispensed to community (78%) or LTC (22%). Most daily oral prescriptions (97%) were dispensed for a typically expected days supply. However, distinct differences were observed for other regimens with the typically expected days supply more common in community vs. LTC: cyclical etidronate (86% community vs. 40% LTC), weekly oral (91% community vs. 60% LTC), and monthly oral (94% community vs. 35% LTC) or nasal spray (84% community vs. 40% LTC). In both settings, annual zoledronic acid infusion was most commonly dispensed as 1-day supply (62%).

Conclusions: Results suggest that there may be significant reporting errors in the days supply field in Ontario pharmacy claims, particularly among prescriptions dispensed in LTC. The variation noted for osteoporosis medications in Ontario are likely indicative of similar reporting errors for other drugs and in other regions. Errors in the days supply field may have significant implications for drug exposure misclassification in pharmacoepidemiologic studies.

145. COX-2 and Non-Selective NSAID Use in Those at Increased Risk of NSAID-Related Adverse Events

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Background: Adverse events related to the use of non-steroidal anti-inflammatory drugs (NSAID) are challenging for optimizing treatment of pain in older people.

Objectives: The aim of this study was to determine the proportion of non-selective (NS) NSAID and cyclo-oxygenase 2 (COX-2) inhibitor use among people with prior history of gastrointestinal (GI) events, myocardial infarction (MI) or stroke.

Methods: A retrospective study of pharmacy claims data between 2007 and 2009 from the Australian Government Department of Veterans' Affairs was conducted involving 288,912 veterans aged 55 years and over. Analgesic drug utilization among veterans at risk of NSAID related adverse events was assessed. Three risk cohorts were identified including veterans with prior hospitalization for GI events, MI or stroke. Poisson regression was applied to test for linear trend over years.

Results: The prevalence of analgesics dispensed in the overall study population was approximately 34% between 2007 and 2009. Paracetamol was the most commonly used analgesic in all three cohorts. COX-2 inhibitors were more widely used than NS-NSAIDS in all veterans at risk – at the end of 2009 the ratio was 5.1% to 2.5% in the GI cohort, 3.6% to 3.2% in the MI cohort, and 3.6% to 2.6% in the stroke cohort.

Conclusions: Although COX-2 inhibitors appeared to be preferred over NS-NSAID in those with a prior history of GI events, 2.5% of patients were still using an NS-NSAID at the end of the study. Consistent with the guidelines most of them were co-dispensed proton pump inhibitors. COX-2 inhibitors were used at slightly higher rates than NS-NSAIDs in those with a prior history of MI or stroke, which is not consistent with guidelines recommending NS-NSAID use. It is important to recognize these patients and to evaluate the risks and benefits of the treatment on an individual basis.

146. Osteoporosis: Preliminary Results of a Treatment Adherence during a Systematic Follow-Up of Fragility Fractures

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Background: Fragility fractures are under-diagnosed and treated. We are at validating a process of a multidisciplinary systematic follow-up approach for osteoporosis using a clinical nurse.

Objectives: The aim of the study was to evaluate the use of antiresorptive agents after enrollment of the patients in the systematic follow-up.

Methods: We enrolled in the last year 300 subjects over 40 years of age who are treated for a fragility fracture at the Montreal Sacré-Coeur Hospital from July 2010 to 2011. After starting a treatment protocol for osteoporosis, they are followed for a 24-months period. They have to complete questionnaires, medical exams and be evaluated on their compliance to treatment. We reconstructed the exposure to preventive medication by using pharmacy claims and the prescription refills in a subset of the cohort.

Results: Among 74 women and 16 men, the average age was 59.7 years. The most common fractures were wrists (n = 42). The average femoral BMD was -1.52 and -1.72 for the vertebra. The pharmaceutical follow-up showed that 12.6% patients were already on antiresorptive agents and 90% of the patients received at least one dispensation after their fractures. About 67% fulfilled their prescriptions in the first week, where only 55.6% were under tritherapy (bisphosphonates, calcium and vitamin D). This rate declined to 32.1% after the third refill.

Conclusions: Preliminary results show that the adherence decreases strongly after the first 3 months. We expect to improve the adherence to antiresorptive agents by having access to pharmaceutical files in real time during the systematic follow-up.

147. Incident Use, Discontinuation and Switching of Antidepressant Drugs in the Rotterdam Study

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Background: Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants are mostly prescribed for the treatment of depression. These different antidepressants are prescribed based on the symptoms, co-morbidities and possible adverse events. Problems with tolerability influence the preference for different antidepressants. Intolerance can result in early discontinuation or switching of treatment.

Objectives: To investigate the pattern of incident antidepressant drug use and the intolerance to antidepressant drugs in the Rotterdam Study in an aging population.

Methods: Participants from the Rotterdam Study between January 1st 1991 and December 31st 2007 were included. Participants were aged ≥45 years and lived in a district of Rotterdam, the Netherlands. Incident use was defined as a first prescription for an antidepressant drug between April 1st, 1991 and December 31st, 2007. Participants with prescriptions within the first 3 months were excluded because they were probably prevalent users. Switching, irrespective of class and discontinuation of treatment was defined within 45 days after the first prescription.

Results: A total of 12,664 participants were included, of which 1,549 were incident users. Incidence increased by age (9.0/1,000 PY at age 50–54 to 21.2/1,000 PY at age 80+), and stayed stable over the calendar years (15.4/1,000 PY in 1991 to 14.1/1,000 PY in 2007). Over the calendar years SSRIs and other antidepressants were more often prescribed as initial therapy, while the initial percentage of TCA prescriptions decreased. 42.8% of these incident users discontinued treatment within 45 days. Users of SSRIs and other antidepressants were less likely to discontinue treatment, compared to TCA users (OR = 0.55 [95% CI: 0.45–0.69]), and OR = 0.66 (95% CI: 0.47–0.93), respectively). SSRI use was associated with an increased risk of switching compared to TCA (OR = 1.96 [95% CI: 1.10–3.49]).

Conclusions: This study showed that the preference for SSRIs and other antidepressants increased over time, and overall incidence increased by age. Compared to TCAs, SSRIs and other antidepressants were associated with a lower risk of discontinuation.

148. Benzodiazepine Exposure and Real-Life Utilization among Elderly: A French Longitudinal Cohort Study

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Background: Benzodiazepines (BZD) utilization is associated with well-identified risks. Recent reports on European psychoactive drugs consumption in 2009 and from Afssaps in 2012 concluded that France was the second

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country consumer in Europe. Thus, French updated data were still needed.

Objectives: This study aimed to determine the prevalence of French BZD exposure and describe the characteristics of BZD users' and their utilization, using the national Insurance Healthcare System (IHS) reimbursement database.

Methods: The French sample (Echantillon Généraliste des Bénéficiaires, 1/97th) of national IHS was queried to assess data on BZD utilization from July, 1st 2006 to June, 30th 2011. Data from subjects covered by IHS who benefited from one or more reimbursed BZD dispensing were analyzed to estimate the prevalence of use in the general French population. Cohort was split into four groups according to BZD indication: anxiolytic (11 BZD) and hypnotic (9), muscle-relaxant (tetrazepam, TZP) and anticonvulsant (clonazepam, CZP). Treatment persistence was estimated through survival analysis and individual daily dose through cumulative quantity dispensed divided by day's supply. An average dose higher than the maximal dose required in the SmPC was defined as off-label.

Results: Prevalence of exposure was estimated to 20.0% of French population and remained stable from 2006 to 2011. Prevalence increased with age and was higher in women (<40 years: 13.4%, >65: 41.3%; vs. men <40: 8.8%, >65: 26.6%). TZP, bromazepam and zolpidem were the three most reimbursed BZD in 2010. Patients treated with anxiolytic, hypnotic and CZP were older (52.3 ± 19.1 vs. TZP: 43.2 ± 15.4 years, $p < 0.05$). Overall treatment persistence was significantly longer for anxiolytic than hypnotic, CZP and TZP (36, 33, 27 and 7 months, respectively). In elderly, off-label dose was found in 14.9% (<40 years: 21.0%, $p < 0.05$); whereas treatment persistence was longer (46.0 [95% CI: 45.2–46.8] vs. <40: 14.4 [13.7–15.0] months).

Conclusions: Risks related to long-term and high degree of exposure to BZD, particularly in elderly, conducted Afssaps to consider novel corrective actions to optimize BZD use (secured prescription form).

149. Antidementia Drugs Utilisation Patterns in Europe: Predictive Factors of Switch and Discontinuation of Cholinesterase Inhibitors in the ICTUS Cohort Study

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Background: Antidementia drugs, despite their moderate efficacy, remain the sole available drugs in Alzheimer's Disease (AD). However, prescribing practices greatly vary among European countries, according to factors related to patient, prescribers, and countries (health policies, national guidances).

Objectives: To describe antidementia drugs prescription patterns across 12 european countries and identify predictive factors for Cholinesterase Inhibitors' (ChEI) switch and discontinuation.

Methods:

Design: The 2-year ICTUS (Impact of Cholinergic Treatment USe) cohort study.

Setting: Of 1,375 mild-to-moderate ambulatory AD patients (MMSE score [10–26]) looked after by an informal caregiver were recruited in 29 AD expert centers during 2003–2005 and followed up twice yearly.

Exposure: ChEI (donepezil, galantamine, rivastigmine) and memantine prescriptions were based on AD center specialist reports. Other drug exposures relied on caregiver reports.

Main outcome measure: switch was defined as a change of ChEI type ($\pm$concomittant memantine initiation) with up to 35 days free of any antidementia drug accepted between strategies. Discontinuation was defined as the discontinuation of any ChEI drug (irrespective of memantine initiation/continuation/discontination) for a period >35 days.

Statistical analysis: Multivariate Cox proportional hazard models were performed to determine predictive factors for ChEI switch and discontinuation among patients treated with ChEI at baseline.

Results: At baseline, 1,201 subjects (87.3%) were treated with a ChEI monotherapy, 21 (1.5%) were on memantine monotherapy, 29 (2.1%) were on bitherapy, and 124 (9.0%) were not prescribed any antidementia drug. The prevalence of ChEI prescription (whether in mono or bitherapy) between countries vary from 79.1% to 100%. Main reasons for ChEI non prescribing at baseline were patient refusal, waiting for further investigation and concomittant disease. Incidence rates and predictive factors of the two events will be presented during ISPE congress.

Conclusions: This study will provide useful data on antidementia drug use patterns in a real life context.

150. Trends in Initiation of Antiparkinsonian Drug Treatment among Patients with Parkinson's Disease in the UK between 1997 and 2010. Are Treatment Recommendations Followed? A Population-Based Analysis

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Background: Between the years 2002 and 2006, a number of treatment recommendations for Parkinson's disease (PD) have been published. Patterns of real-life prescribing behavior for treatment initiation in PD remain poorly documented.

Objectives: To describe trends in initiation of antiparkinsonian drug treatment among patients with PD in the UK between the years 1997 and 2010. To compare prescribing before 2002 with that after 2006 by age category.

Methods: We identified PD patients from UK's THIN database who were 50–89 years of age and newly treated with antiparkinsonian drugs (at least two prescriptions) between the years 1997 and 2010. This was a descriptive analysis. We defined regimens as monotherapy if both first and second prescription were of the same single class of drug.

Results: The analysis involved 6,261 newly treated PD patients (41% female) with a mean age of 73.3 (SD 8.5) years at first antiparkinsonian drug prescription. Time trends are described by comparing the year 1999 with the year 2009 as follows. The percentage of patients who received dopamine agonist monotherapy as initial treatment increased from 13% in 1999 to 45% in 2009 for age category 50–64, while it increased from 3% in 1999 to 12% in 2009 for age category 65–89. MAO inhibitor monotherapy increased from 3% to 14% for age 50–64, while it increased from 2% to 6% for age 65–89. Levodopa monotherapy decreased from 64% to 31% for age 50–64, while it decreased from 88% to 78% for age 65–89. Anticholinergic monotherapy decreased from 8% to 2% for age 50–64, while it decreased from 4% to 0% for age 65–89.

Conclusions: The observed changes in prescribing behaviour for treatment initiation in PD between 1997 and 2010 merit further investigation and critical evaluation. Most of the observed patterns are compatible with published treatment recommendations, e.g., to opt for delay of levodopa therapy in younger patients (by using a dopamine agonist as initial treatment) or to avoid use of anticholinergics in the elderly.

151. Psychotropic Drug Use before and after First Diagnosis of Alzheimer's Disease: An Analysis of German Claims Data

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Background: Alzheimers' disease is a growing health problem in an aging population. The efficacy of anti-dementia drugs is limited and co-medication of psycholeptics is of high risk.

Objectives: The aim of the study was to analyse the use of these drug groups (before and) after diagnosis of Alzheimers' disease.

Methods: Data base: claims data of a large German statutory health insurance fund (AOK, federal state of Hesse). Persons 50+ years of age continuously insured from July 2004 to June 2009 plus persons deceased 2007 or later N = 117,163. Study population: Patients with validated diagnosis of Alzheimers' in 2007 (ICD 10-code: F00, G30) without diagnosis of dementia (ICD: F00–F03, F05.1, G30) or anti-dementia drug (ATC code: N06DA, N06DX01) within 3 years before: n = 321, mean age in years 80.7, women: 65%. Controls matched by sex, age, Charlson co-morbidity index, quarter of death 3 years before first documentation of diagnosis. Observation period: eight quarters at 91 days each before and four quarters after diagnosis. Analysed drugs: psycholeptics (ATC: N05), anti-dementia drugs (N06DA, N06DX01).

Results: Within first year after diagnosis 117 patients (36%) received anti-dementia drug, 80% within 90 days after diagnosis. One third started medication with memantine. In 42% of the patients a neurologist or psychiatrist issued the first prescription. The percentage of Alzheimers' patients receiving psycholeptics considerably rose already 2 years before diagnosis and during first year after diagnosis whereas the treatment prevalence in the control group remained constant (8th quarter before diagnosis: 14%, 1st quarter after diagnosis: 37%; controls 8% each). The most often prescribed subgroup was "antipsychotics" (N05A).

Conclusions: Anti-dementia drugs are prescribed cautiously. Patient with dementia differ in use of psycholeptics already 2 years before incidence of dementia. Psycholeptics are frequently prescribed especially in women. As studies showed an excess mortality for dementia patients taking antipsychotics, this indicates a relevant health problem.

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152. Dementia Mortality Rates and Cholinesterase Inhibitors Consumption in Castilla y Leon (Spain). An Ecologic Study

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Background: Cholinesterase inhibitors drugs and memantine are used worldwide for prevention and treatment of dementia. Their effectiveness in reducing disease progression is unclear; however, life expectancy has increased after the introduction of these drugs in 1997.

Objectives: To learn the effect of cholinesterase inhibitor drugs upon mortality in dementia patients.

Methods: An ecologic study has been conducted for the purpose, spanning from 1999 to 2008. Consumption data were obtained from the CONCYLIA database (Sistema de Información de Farmacia. Gerencia Regional de Salud de Castilla y León). Dementia mortality rate was obtained from a hospital discharge database (CMBD-H). A linear regression analysis was performed to learn the relationship between dementia mortality rates and cholinesterase inhibitor and memantine use; R^2 and Pearson's correlation coefficient were calculated.

Results: From 1999 to 2008, dispensed prescriptions of cholinesterase inhibitors and memantine showed a 10-fold increase from 0.5 DDD/1,000 to 5.0 DDD/1,000 inhabitant-day. During the same period, age-standardized dementia mortality rate declined from 10.9 to 9.0 deaths per 100,000 inhabitants. When a linear regression was performed to examine the relationship between dementia mortality rate and consumption of cholinesterase inhibitors for the years considered, R^2 value was 0.60 and Pearson's correlation coefficient value was -0.76. Interestingly, in 1997 after the introduction of cholinesterase inhibitor drugs, dementia mortality rate trend changed and began to decline.

Conclusions: Cholinesterase inhibitor and memantine consumption increased along the period studied. Though different factors may contribute to the decline in mortality in patients with dementia, a mild effect of these medications cannot be ruled out.

153. Antipsychotic Drug Prescribing to Patients on Anti-Dementia Drugs in a South African Patient Population

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Background: It was reported that the black box warnings issued by the FDA regarding the use of atypical antipsychotics for the treatment of dementia resulted in a significant decline in their use for treating dementia symptoms in elderly patients in the USA. No data are available for South Africa.

Objectives: To determine the prescribing of antipsychotic drugs to patients on anti-dementia drugs in a South African private sector patient population.

Methods: A retrospective, cross-sectional drug utilization study was conducted on prescription data of a national community pharmacy group in South Africa for 2010.

Results: A total of 1,231 patients were prescribed anti-dementia drugs. The average age of patients was 75.10 (SD = 10.27) years, with more than half (56.13%) females. A total of 5,264 prescriptions for anti-dementia drugs was prescribed at a cost of R3074487. Donepezil accounted for 45.84% of prescriptions for anti-dementia drugs, followed by memantine (36.51%), galantamine (17.25%) and rivastigmine (0.40%). Differences were observed between females and males with respect to prescribing frequency ($\chi^2 = 48.491$; d.f. = 3; $p < 0.0001$). Patients received on average 4.28 (SD = 3.77) prescriptions for anti-dementia drugs over the year. Most patients (94.31%) received only one active ingredient. Of those who were prescribed combinations, donepezil in combination with memantine was the most frequently prescribed. Nearly a quarter of patients (23.23%) received one or more antipsychotic drugs despite the black box warnings issued by the FDA and a warning in December 2008 by the South African MCC that antipsychotic drugs are best avoided in patients with dementia of the Alzheimer's type. Slightly more females were prescribed antipsychotic medication. The average age of patients co-prescribed antipsychotic drugs was 71.69 (SD = 14.44) years. Risperidone was the most often prescribed (53.16%) followed by quetiapine (31.10%). Older generation antipsychotics, such as haloperidol, were also prescribed.

Conclusions: Despite serious warnings by health authorities, nearly a quarter of patients on anti-dementia drugs in this patient population still received antipsychotic drugs in 2010.

154. Potentially Inappropriate Medication Use among Patients with Alzheimer Disease in REAL.FR: Be Aware of Atropinic and Benzodiazepine Drugs!

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Background: Quality of prescriptions among elderly people has been often studied, especially with several lists of

potentially inappropriate medications (PIM). However, pharmacoepidemiological studies have investigated PIM in Alzheimer Disease (AD) patients.

Objectives: To assess the prevalence of PIM use in community-dwelling patients diagnosed with mild to moderate AD patients and to identify the clinical factors associated with prescription of PIM.

Methods: REAL.FR is a four-year, prospective, multicenter cohort of AD patients. We analyzed baseline data of AD patients. Drug intake was collected through caregiver report and analysed using Laroche and Beers PIM list. A logistic regression was conducted.

Results: Of 684 AD patients were included (mean age 77.8 ± 6.8, 71.0% females). Most of them (89.0%) were treated with cholinesterase inhibitors (none with memantine). Forty-six percent of the patients required assistance with activities of daily, and 26% lived alone at home. Over half of the patients (52%) had an income upper than 1,500 Euros and most of them (84%) were followed in Geriatric centers. High-level polypharmacy (≥7 medications) was identified in 24% of patients. Respectively 46.8% (95% CI: 43.0–50.5%) and 25.3% (95% CI [22.0–28.6%]) of the patients had at least one PIM using Laroche list or 2003 Beers list. Cerebral vasodilators were the most used drugs with 24.0% (95% CI [20.9–27.3%]) of the total prescriptions. Users of atropinic drugs were 17.0% (95% CI [14.1–19.8%]). Benzodiazepines with long half-life were prescribed to 8.5% of the sample (95% CI [6.4–10.6%]). Drugs with atropinic properties and cholinesterase inhibitors were associated in 15.9% (95% CI [13.8–18.2%]). In multivariate analysis, only Activities of Daily Living (ADL) (superior 1 incapacity) and income (inferior 1,500 Euros) were associated with PIM prescription.

Conclusions: This study shows that PIM prescription concerns around 1 out of 2 AD patients. Among these drugs, cerebral vasodilators, atropinics and benzodiazepines were the most used.

155. Influence of Patient, Physician, and Hospital Characteristics on Oxaliplatin Receipt among Older Stage II and III Colorectal Cancer Patients in the US

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Background: The US Food and Drug Administration approved oxaliplatin for the adjuvant treatment of resectable stage III colon cancer in November 2004. Yet, few studies have examined patterns of oxaliplatin use in routine practice, particularly among older patients and those with an off-label indication (stage II colon or stage II/III rectal cancer).

Objectives: To identify patient, physician, and hospital predictors of oxaliplatin receipt from 2004 to 2007.

Methods: All individuals diagnosed at age >65 with stage II or III CRC from 2004 to 2007 who underwent surgical resection and received chemotherapy were identified using cancer registry data linked to Medicare claims and enrollment records. These data included information on patient demographics, tumor features, and hospital characteristics. Physician information was obtained from the American Medical Association. Poisson regression accounting for non-nested clustering was used to identify independent predictors of oxaliplatin receipt, stratified by on-/off-label indication. Analysis of the area under the curve (AUC) assessed the contribution of measured characteristics on explained variation in oxaliplatin use.

Results: We identified 4,819 individuals who underwent surgical resection at 795 hospitals and received chemotherapy from 1,579 physicians. Overall, 52% received oxaliplatin, 56% for on- and 29% for off-label indications. Individuals who were older, diagnosed prior to 2007, or separated, divorced, or widowed vs. married were less likely to receive oxaliplatin, while those diagnosed with colon vs. rectal cancer or stage III vs. II disease were more likely to receive oxaliplatin. Findings from stratified analyses were similar. After accounting for calendar year, patient factors comprised most of the explained variation in oxaliplatin receipt (full model AUC: 77.6%; calendar year model AUC: 66%; patient + calendar year model AUC: 77.5%).

Conclusions: Oxaliplatin use increased rapidly from 2004 to 2007. Measured patient, as opposed physician or hospital, characteristics drove most of the remaining variation in oxaliplatin use.

156. Bevacizumab for Neovascular Age-Related Macular Degeneration

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Background: Age-Related Macular Degeneration (AMD) is a common cause of irreversible blindness among the elderly worldwide. Vision loss results from the abnormal growth and leakage of blood vessels in the macula, a specialized portion of the retina which is responsible for optimal visual acuity. Without this macular vision, patients become legally blind. Vascular endothelial growth factor (VEGF), the cytokine primarily responsible for blood-vessel growth, is inhibited when anti-VEGF drugs are injected repeatedly into the eye, and blindness is prevented in the majority patients. Because of the significant

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difference in cost compared to ranibizumab, bevacizumab is used off-label to treat AMD.

Objectives: To evaluate the best scientific evidence currently available regarding the efficacy and safety of bevacizumab for the treatment of neovascular AMD.

Methods: In order to identify systematic reviews and randomized clinical trials (RCT) published in English, Portuguese, and Spanish, a wide search in the following databases was performed: MEDLINE (Pubmed), Cochrane Library, Tripdatabase, and the CRD.

Results: Three RCT studies were selected, demonstrating equivalence with functional and structural improvements between bevacizumab and ranibizumab. In the CATT Research Group's study (2011), after 1 year, both had equivalent effects on visual acuity when administered according to identical schedules. The proportion of patients who experienced serious systemic adverse events was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% IC 1.01–1.66). However, the study does not have sufficient statistical power to correlate the events to the medication.

Conclusions: Based on the results of the CATT study and global experience, the New England Journal of Medicine published an editorial supporting the use of ranibizumab and/or bevacizumab for the treatment of neovascular AMD. In addition, the National Health Surveillance Agency (ANVISA) published a technical report concluding that both can be used as equal alternatives in terms of efficacy, however safety data for bevacizumab are insufficient. Therefore, the establishment of a Pharmacovigilance Programme specific to bevacizumab is suggested.

157. Prevalence and Associated Factors of Food Supplement Use in Community Dwelling Population over Age of 50 in Ireland

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Background: Despite easy access to various food supplements and their potential for beneficial and adverse effects, little is known about their utilisation and concomitant use with medicines in older population of Ireland.

Objectives: To determine the prevalence of food supplement use in adults aged 50 and over and to identify the associated factors for their use.

Methods: Data from The Irish Longitudinal Study on Ageing (TILDA) which included 8,175 community dwelling participants aged 50 or more who provided social, economical and health data. Their prescription and non-prescription medications, vitamins, herbal and alternative medicines that were taken "on a regular basis, like every day or every week" were recorded. For 94 participants no data was obtained and 8,081 participants (98.9% participation rate) data was analysed. Ethical approval was been obtained. Food supplement use was compared across the gender and age groups (50–64, 65–74 and 75 years and more). Proportions were presented as percentages including 95% confidence interval (CI). Group differences were assessed with Pearson's chi-square test, correlation between different variables and medicine and/or food supplement use with logistic regression.

Results: Of 10.1% (95% CI 9.2–11.2%) of men and 23.5% (95% CI 22.3–24.8%) of women reported use at least of one food supplement. Use was significantly different as between sexes in all age groups (50–64, 65–74, 75 and over) as between age groups alone ($\alpha = 0.05$). Concomitant use of food supplements with medicines was reported in 8.6% (95% CI 7.8–9.6%) of men and 19.7% (95% CI 18.5–20.9%) of women and was significantly higher in women in all age groups. Food supplement use was correlated to being a women, retired, middle class, well educated, non-smoker having at least one medicine and chronic disease.

Conclusions: Use of food supplement is wide in Irish population, especially in elderly. Typical user has at least one chronic disease and taking medicine(s) and is prone for possible risk of medicine-food supplement interaction.

158. Medication Review in Polypharmacy Patients

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Background: Patients in concomitant use of multiple drugs, polypharmacy (PP), are at increased risk of significant events, side effects, interactions and insufficient treatment outcomes. The general practitioner (GP) may apply several guidelines without prioritizing, and may not be aware of all the patients' medications, or of the drugs' interactions.

Objectives: Investigate the prevalence of PP at the national level and in the participating general practices.

Investigate resons behind PP through medication review in general practices and in one nursing home.

Provide proposals for more rational treatment and reduce the prevalence of PP.

Develop a tool for monitoring PP and the effects of medication reviews.

Methods: We performed systematic medication reviews by pharmacist and a specialist in internal medicine for PP patients (patients treated with >5 drugs at the 5th ATC level between July 1 and December 31 of 2009) selected by the GPs in 17 general practices and in one nursing home. For each drug the pharmacists registered the indication, recommendations for change of medication and the reason for each recommendation.

Results: Thirteen percent of the Danish population was PP-patients (range 6–51) during the second half of 2009. Fifty-eight percent of drug costs in primary care were attributed to this patient group. One third of the PP-patients were treated with ten or more drugs. We performed medication reviews for 65 patients in general practice and 34 patients at the nursing home. We recommended changes to 30% of the medications in general practice and 18% at the nursing home. In both places "cessation" constituted about half of the recommendations. At the nursing home 86% of the proposed cessations were performed succcesfully. On average the PP-patients in general practice were treated with 12 different drugs, while PP-patients in the nursing home were treated with eight drugs. Prescribing MDs' lack of information about the patient's current medications constitutes an important barrier to rational pharmacotherapy.

Conclusions: Interdisciplinary medication review results in more rational drug treatment. Each medical record should include an up-to-date list of the patient's medications.

159. Risk Factors for Co-Medication of Contraindicated Drugs in Hospitalized Elderly Patient

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Background: Elderly patients usually have multiple chronic diseases, thus they are prone to be exposure to multiple co-medications, and increased chance to have drug-drug interactions (DDIs). However the risk factors for co-medication of contraindicated drugs are not well defined yet.

Objectives: To reveal the risk factors associated with co-medication of contraindicated drugs in hospitalized elderly patients.

Methods: This study was designed as a case-control study. Elderly patients (> 65 years) hospitalized to a Korean tertiary teaching hospital was enrolled to the study between June 1, 2010 and May 31, 2011. All of the medication in the hospital was monitored by a DDI alert system. Thus the case was defined who having received at least one co-medication of contraindicated drugs during hospitalization even after the alert for possible DDIs. The control was defined who did not received any co-medication of contraindicated drugs with/without DDI alerts. Logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), after adjusting for age, gender, length of stay, number of medications and number of diagnoses.

Results: Of the 6,423 study population, 257 (4.0%) was enrolled to case group and the others enrolled to control group. Based on multivariate analysis, male sex (OR 1.48, CI 1.13–1.92), day of hospital stay (OR 1.02, CI 1.01–1.02), number of diagnoses (OR 1.06, CI 1.03–1.09), and number of medications/day (OR 1.02, CI 1.01–1.02) were revealed to be related with co-medication of contraindicated drugs in hospitalized elderly patients. Frequent co-medications of contraindicated drugs were: co-medication of anti-inflammatory drug (532, 30.3%), antibacterials + antiepileptics (346, 19.7%), and anti-inflammatory drug + antithrombotic agent (232, 13.2%) in orders.

Conclusions: Risk factors associated with co-medication of contraindicated drugs for hospitalized elderly patients were revealed. Listed combination of frequently co-prescribed drugs, the combination of which are contraindicated, should be closely monitored to prevent possible adverse drug events.

160. Oxycodone Use in Australian Veterans at Risk of Respiratory Depression

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Background: The risk of respiratory depression from opioid-treatment may be particularly high in patients with underlying respiratory conditions or in those receiving concurrently other medicines that can contribute to respiratory depression.

Objectives: This study examined dispensing patterns of oxycodone in Australian veteran population with chronic respiratory disease and in those receiving other medicines that may contribute to respiratory depression.

Methods: An observational retrospective study was undertaken using Australian Government Department of Veterans' Affairs dataset with pharmacy claims for approximately 300,000 veterans and their dependants. The veteran population have slightly more visits to general practitioners (RR: 1.17, $p < 0.05$) and hospitalisations (RR: 1.21, $p < 0.05$) annually than the general Australian population aged ≥40 years.

Monthly rates of oxycodone use were determined from 2007 to 2010 amongst: 1. veterans with chronic respiratory disease (defined as patients dispensed medicines for chronic obstructive airway disease), and

2. veterans dispensed medicines that may cause respiratory depression (defined using the Australian Medicines handbook and MicroMedex) – other opioid analgesics, antipsychotics, muscle relaxants, anxiolytics, hypnotics, sedatives, antiepileptics and sedating antihistamines.

Poisson regression models were used to test for linear trend over time in prescription rates.

Results: There were 22,844 veterans with chronic respiratory disease in January 2007 with mean age 81 (SD 8). Oxycodone utilization increased from 3.1% to 5.9% over the study period (slope of trend line = 1.159; 95% confidence interval (CI) 1.14, 1.18, $p < 0.0001$) in those with chronic respiratory disease.

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77,989 veterans were taking medicines that may cause respiratory depression in January 2007 (mean age 79, SD 11). Oxycodone utilisation increased from 4.5% in January 2007 to 8.2% in December 2010 (slope = 1.162; 95% CI 1.14, 1.18, p < 0.0001).

Conclusions: Australian guidelines recommend opioids to be used with extreme caution in patients with respiratory depression, asthma or decreased respiratory reserve. Despite this, increasing trends of oxycodone use were observed among veterans at risk.

161. Identification of COPD Patients in Epidemiological Studies Using Administrative Databases

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Background: According to the Global Burden of Disease Study chronic obstructive pulmonary disease (COPD) will account for 6 million deaths per year in 2020. This will move COPD from the sixth-leading cause of death worldwide in 1990 to the third-leading in 2020. COPD, therefore, is of paramount importance for social insurance institutions. Identification of COPD patients using social insurance data, however, is difficult, especially when patients suffer from mild or moderate illness and have not yet received a COPD diagnosis.

Objectives: This investigation aims at compiling methodological approaches applied in claims data analyses and intends to establish an appropriate algorithm for the detection of COPD patients in routine datasets.

Methods: A systematic review of the international literature on epidemiological COPD studies using administrative databases was performed. The MedLine search encompasses publications since 01/01/2000 in English or German language.

Results: The search yielded 43 publications. After assessment of titles, abstracts, and full-texts, 12 of them could be included in the review. The underlying studies chose various approaches for the identification of COPD patients. In most studies, a combination of diagnostic information (i.e., inpatient and outpatient diagnosis codes) and prescription data for COPD-related drugs was used. The minimum age of beneficiaries varied between 18 and 66 years. Prevalence rates ranged from 22% to 48%. Based on the identification algorithms found in the publications and on personal experience with claims data analyses, a revised methodological approach has been developed.

Conclusions: Administrative databases may provide valuable epidemiological insight into COPD. Results, however, vary substantially due to differing definition criteria and methodological diversity. A gold standard for the definition of COPD patients in routine data of statutory health insurance funds is still lacking. Validation studies referring to clinical parameters such as lung function criteria should be encouraged.

162. Prior Pneumococcal Vaccination and Hospitalization for Community-Acquired Pneumonia in Elderly Veterans

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Background: Limited evidence found prior pneumococcal vaccination (PPV) was associated with better inpatient outcomes for pneumonia, but none of the studies focused on elderly patients.

Objectives: To examine the effect of prior PPV vaccination on inpatient outcomes in elderly veterans hospitalized for community-acquired pneumonia (CAP).

Methods: This was a retrospective cohort study of elderly veterans (≥65 years) admitted to VA hospitals for CAP between October 1, 2002 and September 30, 2003 (FY'03), excluding those transferred from another hospital or nursing homes. The first CAP admission in FY'03 ("index admission") were identified via the principal diagnosis of pneumonia (ICD-9 codes 481.xx–487.0x). All patients had ≥1 VA outpatient visit each year in the 5 years before the index admission and were classified into 4 groups: PPV only, flu shot only, both, or none. PPV status in the 5 years prior and flu shot status in the previous year were determined using ICD-9 V-codes, procedure codes, or CPT codes. The outcomes were (primary) inpatient mortality and length of stay and (secondary) respiratory complications. Cox-proportional hazards and logistic regression analyses were used to assess the impact of prior PPV and flu vaccination on length of stay, inpatient mortality, and respiratory complications during the index admission, controlling for patient demographic and clinical characteristics.

Results: Of 6,723 elderly patients were included. Of 1,347 (20%) had only PPV, 1,698 (25%) had only flu shot, 1,668 (25%) had both, and 2010 (30%) had neither. After

adjusting for baseline characteristics, having prior PPV alone, flu shot alone, or both did not significantly affect the risk of inpatient mortality or development of respiratory complications, compared to patients without vaccination. However, prior flu shot alone (AHR: 1.11, 95% CI: 1.04–1.19) or both (AHR: 1.13, 95% CI: 1.06–1.21) significantly reduced length of stay.

Conclusions: Prior PPV alone may not reduce either the risk of inpatient mortality or length of stay for elderly patients admitted for CAP. However, prior vaccination may be underidentified in the study and future research is needed to confirm the finding.

163. Inappropriate Prescribing in Elderly Patients in a Brazilian Nursing Home

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Background: The elderly Brazilian population is growing rapidly and represents today 11% of the total population. This development on Brazil's demographic profile involves the reduction on the incidence of infectious and parasitary diseases and the increase of chronic diseases prevalence, typical of the elderly, which enhance the health demand for specialized services (like nursing homes-NH) and for drugs.

Objectives: To determine the profile of potentially inappropriate medication (PIM) use and prescribing omissions (PO) among elderly in NH.

Methods: Observational study carried in a NH of Divinopolis, Brazil. The population comprised individuals aged 60 years or more residing in the NH. Drug prescriptions of August 2010 were reviewed in order to identify the use of PIM according to the Beers Criteria and the STOPP (Screening Tool of Older Persons' Prescription), PO according to the START (Screening tool to Alert to Right Treatment), and polypharmacy (use of five or more drugs). Association between polypharmacy and PIM prescription was assessed using bivariate analyses (odds ratio with 95% confidence interval and Pearson's Chi-square test). The Mann–Whitney U-test was used for median comparison. A 5% significance level was defined for every comparison.

Results: Of 46 residents (mean age 80.5 ± 8.5 years) were included in the study. Sixty-one percent of them were female, 37% received at least one PIM according to Beers Criteria (n = 17) and 60.9% according to the STOPP (n = 288). A statistically significant difference was found between the medians of number of PIM detected with the STOPP and the Beers Criteria ($p = 0.006$). PO were identified among 17.4% of the elderly (n = 8). Polypharmacy was found to be associated with the PIM use according to the Beers Criteria ($p < 0.05$), but not according to the STOPP ($p = 0.097$).

Conclusions: The high number of inappropriateness detected paints an intricate scenario and indicates the existence of a low level pharmacotherapy in the NH. It shows the need of work towards elderly drug therapy upgrade by knowledge forecast among physicians about tools that should be used to improve geriatric prescriptions.

164. Nationwide Variation in Nursing Home Antipsychotic Use, Staffing and Quality of Care

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Background: Nearly one-third of US elderly nursing home (NH) residents receive atypical antipsychotics despite warnings from the US Food and Drug Administration about marginal clinical benefits and serious adverse effects including stroke and death associated with these drugs in older adults with dementia.

Objectives: To provide a nationwide picture of patterns of atypical antipsychotic use (and associated medication costs) in NHs to assess if variation in use is associated with NH staffing or quality.

Methods: We linked a nationwide dataset of resident-level prescription drug claims (2009–2010) to federal web-based report card Nursing Home Compare database. Design: A cross-sectional study in 5,137 NHs with 561,681 residents. Exposure: NH-level use of atypical antipsychotics, state-level annual spending on atypical antipsychotics in NHs.

Main outcome measures: Probability of receiving below/much below average report card ratings in: Overall Quality, Health Inspections, NH Staffing, and Quality Measures (10 resident-level assessments); total licensed staff, RN hours and CNA hours per resident day. Statistical Analyses: We arrayed NHs into lowest (0–14.7%) to highest (33.1–100%) use quintiles and tested for associations using logistic and regression models, adjusted for age, gender and state.

Results: NHs in states in lowest use quintile spent on average half as much on atypical antipsychotics as compared to NHs in states in highest use quintile ($436 per resident; 95% CI: 425–447 vs. $835, 853–874. Relative to NHs in lowest use quintile, NHs in highest use quintile were significantly more likely to receive below/much below ratings in NH staffing (AOR 1.35, 1.08–1.68), health inspections (AOR 1.25, 1.02–1.52), and overall quality (AOR 1.36, 1.11–1.67). No association was detected in the 10 specific quality measures. NHs in highest use quintile had significantly less staff than NHs in

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lowest use quintile: 1.37 licensed staff, 1.36–1.37 vs. 1.59, 1.58–1.59; .58 RN hours, .58-.57 vs. .77, .76-.77; 2.28 CNA hours, 2.27–2.28 vs. 2.52, 2.51–2.52.

Conclusions: Significant variation exists in use of atypical antipsychotics in NHs, and NH-level factors particularly staffing may be driving this range.

165. Overview of Drug Use among the Elderly in Japan Using IMS Prescription Database

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Background: Elderly individuals prone to use multiple medicines for treatment of comorbidities. Consequently, polypharmacy may be associated with the increase of health risk due to drug interactions and the decrease of treatment adherence. The information on characteristic of patients with polypharmacy is scarce. The drug utilization research (DUR) was previously conducted to monitor patients by community pharmacies in Hiroshima in 2009.

Objectives: To understand the profile of the elderly patients with polypharmacy, comparing to the findings of the previous DUR.

Methods: This is a cross sectional research using a secondary database of IMS NPA™ Family (IMS Japan K.K.) which includes prescription information collected from community pharmacies. Prescription data of patients aged 60 years and older, from April 2009 to March 2010, were extracted from pharmacies in Hiroshima, Japan. A descriptive analysis was conducted to see patient backgrounds, profile of polypharmacy, and drug use trend throughout the year. Polypharmacy was defined as receiving 5 or more drugs for internal use during 1 month.

Results: During the study period, 34,608 (Male 45%, Female 55%) patients visited the registered community pharmacies to receive internal medicines. Average numbers of prescription drugs were 8.6 per year per person (SD = 11.0 Median = 5), and 4.2 per date of distribution per person (SD = 3.3 Median = 3), respectively.

The most frequently distributed drug from pharmacies was Calcium channel blocker (7.6% of total drug record), and followed by Angiotensin II antagonists (4.8%) and Lipid modifying agents (4.4%). The drugs for acid related disorders were distributed to the majority of patients (42.3% of the total population), and received by 72.7% of Antiflammatory and antirheumatic products users. Throughout the year, 31.1% of the elderly patients were exposed to polypharmacy.

Conclusions: The elderly patients with polypharmacy showed a drug use pattern which was similar to the other DUR. Other information including health and living condition was not investigated in this research, and is to be considered in the future research to explore factors of polypharmacy and to contribute a good medication practice.

166. Polypharmacy in the Elderly: A Deeper Analysis of Drug Utilization in Sweden and Germany

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Background: Polypharmacy, i.e., use of many drugs at the same time, is common in the elderly and may be associated with negative consequences. Some examples are a higher risk of drug-drug interactions and side effects and a lower patient compliance. The number of drugs defining polypharmacy varies between different studies. But what does the number really tell?

Objectives: The aim of this study was to analyze which substances that were most frequently prescribed to elderly with excessive polypharmacy (use of 10 or more drugs) in Sweden and Germany.

Methods: A cross-sectional observational study was done using individual based drug dispensing data on elderly 65 years and older from the Swedish Prescribed Drug Register (1.4 million elderly) and Germany's (AOK) drug register (5.3 million elderly). Period prevalence for the time interval October to December 2010 was calculated. The proportion dispensed different substances was compared between patients with polypharmacy and those dispensed < 10 drugs.

Results: A total of 180,000 elderly (13% of all elderly dispensed drugs) were dispensed more than 10 different substances. The corresponding figure in Germany were 438,000 (8%). In Sweden the most common drugs for this population were paracetamol (56% of patients with excessive polypharmacy), acetylsalicylic acid (52%) and furosemide (42%), in Germany the use of torasemide (35%), simvastatin (35%) and pantoprazole (33%) dominated. A majority of all drugs commonly used in polypharmacy patients were recommended in national guidelines. However, some inappropriate drugs were identified and there were large differences between the countries in, e.g., the use of NSAIDs, analgesics and antidepressants.

Conclusions: When assessing drug use in terms of polypharmacy, the focus should not lie on the amount of drugs; the importance is which drugs are administered. Through international comparisons strengths and weaknesses of different countries' drug treatment of the elderly can be found. Differences between the countries can partly depend on how common a disease is in a country, but also which drugs are available as OTC-drugs and the availability of guidelines/formularies.

167. Feasibility of a Novel Data Source for Drug Utilisation Research in Aged Care

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Background: Drug utilisation studies are highly dependant on the quality and completeness of the data set used. Like many countries Australia there are a number of administrative data sources which can be used to explore drug utilisation in populations. Commonly used Australian data sources include government reimbursement data, pharmacy dispensing data or physician prescribing data; however these datasets may not contain complete medication histories for individual patients. Dose administration aids (DAA) are used in Australian nursing homes to facilitate medication administration and safety. The associated DAA administrative data includes information on all medicines administered patients receiving DAAs.

Objectives: The objective of this study was to explore the feasibility of using dose administration aid packing data to determine the prevalence and type of medication use in aged care facility residents.

Methods: A cross sectional survey was conducted of medication use by residents from 26 aged care facilities in NSW, Australia was conducted using DAA packing data. Residents (n = 2,585) who received at least one prescribed medication between June 31,2009 and 1 July 2010 were included in the analysis. The primary outcome measure was the prevalence of prescribed medication use (% patients). The top 10 medications by ATC class (level 5) were determined.

Results: The most commonly used classes of medications were nervous system agents (ATC class N, 89% of the study population), alimentary tract agents (ATC class A, 88%), and anti-infectives (ATC class J, 63%). The top 10 medications used were paracetamol (75%), senna combinations (47%), vitamin D (40%), cephalexin (35%), furosemide (30%), macrogol laxatives (30%), low dose aspirin (28%), temazepam (27%) and eye lubricants (21%).

Conclusions: Dose administration aid packing data represents a novel data set well suited for use in drug utilisation research. The completeness of the data and the inclusion of both prescription and non-prescription items provides unique opportunities for drug utilisation research and pharmacoepidemiology.

168. Drug Use Pattern and Drug Related Problems in Elderly People with Dementia in Sweden

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Background: Prevalence of dementia is high among the elderly population in Sweden, almost 1% at the age of 60 years. Prevalence of drug related problems (DRPs) is high in nursing home populations. Cognitive disturbances make individuals with dementia even more susceptible to DRPs.

Objectives: To determine the drug use pattern and DRPs in elderly people with dementia living in nursing homes.

Methods: Drug utilization reviews were conducted in all patients in residential dementia care homes in the municipality of Linkoping, Sweden excluding patients in the terminal stage of life. Data on the patients' body weight, symptoms, creatinine value and diagnoses were provided by a nurse. The reviews were undertaken by pharmacists based on these data together with clinical judgement, and local and national guidelines. DRP was defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes. Drug use pattern and DRPs were discussed in a multidisciplinary case conference and interventions were planned to resolve the problems. The prescribed drugs were analyzed before the case conference and after 7–9 months.

Results: A total of 265 drug utilization reviews were performed at 22 dementia care homes. On average each patient used 9.0 drugs (7.4 on a regular basis) and the most common drugs were analgesics and antipyretics (66%), laxatives (57%) and anxiolytics (52%). In total 562 DRPs (2.1 DRPs per patient) were identified and the most commonly classified DRPs were lack of indication for treatment (41%) and dosage too high (10%). The most common interventions were drug cessation (42%) and decrease in dose (18%). After 7–9 months the average number of drugs were 8.7 (7.0 on a regular basis). The principal changes in drug use after the follow-up was observed for anti-dementia drugs (-18%), opioids (44%) and high-ceiling diuretics (22%).

Conclusions: The results indicate that the number of drugs is high among individuals with dementia in nursing homes. Analgesics and anxiolytics are common drugs. High numbers for the DRP lack of indication for treatment imply substandard documentation for drug treatment.

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169. Medication Reviews of Patients Using Drugs Most Frequently Involved in Drug Related Hospital Admissions

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Background: In the Netherlands in 2008 specific recommendations were launched to prevent hospital admissions related to medication. Medication Reviews (MR) were suggested for susceptible patients.

Objectives: To determine implementation of pharmacist led Medication Reviews (MRs) and its effects on use of drugs with increased risk for hospital admissions (HARMs).

Methods: From January 2009 to June 2011 we performed an observational study in Dutch community pharmacies. Fidelity of Implementation for completing MRs was measured. Drug dispensing data, related to patients aged ≥65 years with ≥5 drugs in chronic use, were used to identify changes in drug related risks (HARM items) in patients selected for MRs (cases) between baseline and follow-up and compared to eligible, non-selected patients within volunteering pharmacies (controls).

Results: In 278 volunteering pharmacies, 102 pharmacies selected a total of 1,661 patients. MRs were completed in 59% of these patients. Cases had an average of 0.33HARM items at baseline compared to 0.28 in controls. At follow-up mean number of HARM items decreased in cases by 0.05 (0.09 in patients with complete MR) and 0.07in controls. Between-group differences were not significant.

Conclusions: Implementation of pharmacist led MRs was suboptimal, which might explain the non-significant effects. New strategies to enhance implementation fidelity of MR are needed to realize its full potential.

170. The Effects of Abrupt Antipsychotic Discontinuation in Cognitively Impaired Hospitalised Elderly: A Pilot Study

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Background: The off-label use of antipsychotics for behavioural and psychological symptoms of dementia (BPSD) is controversial. Guidelines advise to minimise antipsychotic use in cognitively impaired elderly given the adverse effects and limited efficacy, and to undertake discontinuation.

Objectives: To explore the feasibility of abrupt discontinuation in older hospitalised adults with cognitive deterioration using antipsychotics, and to explore the effects with regard to withdrawal phenomena, re-occurrence of neuropsychiatric symptoms, and relapse to antipsychotics over time.

Methods: A pilot study with 40 hospitalised geriatric and cognitively impaired patients using antipsychotics for BPSD, in which the effects of abrupt antipsychotic discontinuation were investigated using neuropsychiatric inventory (NPI) scores before and 1 month after discontinuation. Withdrawal symptoms were monitored using a checklist during five consecutive days after abrupt discontinuation.

Results: Study participants (n = 40) were in 53% male, with a mean age of 84 years (range 67–95 years). The total mean baseline NPI score was 21 (SD 12) with mainly behavioural rather than psychological disturbances. After abrupt discontinuation, mild withdrawal symptoms were observed in 72% of the patients, with frequencies of symptoms peaking on day 2 (53%) and day 3 (48%).

After 1 month, 31 patients (85%) were still off antipsychotics and improved on the majority of NPI domains, with a total mean NPI score decreasing from 18 (SD 13) to 12 (SD 8, p = 0.003). In the relapse group, there was no deterioration associated with the abrupt discontinuation and subsequent resumption of therapy, with a total mean NPI score after 1 month decreasing from 31 (SD 8) to 27 (SD 12, p = 0.345).

Conclusions: Abrupt antipsychotic discontinuation in elderly with BPSD is feasible with a high success rate. Discontinuation efforts are needed to differntiate between patients in which continuing antipsychotics have no added value, and patients in which continuing treatment may be justified.

171. The Prevalence of Potentially Inappropriate Prescribing in Older Patients Presenting to an Emergency Department Following a Fall

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Background: Certain classes of medication are known to significantly increase the risks of falls in older patients. Prescribing criteria that define potentially inappropriate prescribing (PIP) for older people include the Beers and the STOPP/START criteria. PIP is one of the factors associated with preventable falls in older persons.

Objectives: To assess: (i) the prevalence of PIP in a cohort of older patients presenting to the Emergency Department (ED) following a fall and (ii) whether there were sustained changes in prescribing in this group following this event.

Methods: All patients 70 years and over who presented to the ED of a large teaching hospital with a *fall* as the primary complaint over a 12 month period (January 2010–December 2010) were included. Medication in the 12 months pre- and post-presentation with a fall was identified using the HSE-Primary care reimbursement services (PCRS) pharmacy claims database. Prescribing criteria for PIP including the STOPP/START and Beers criteria were applied. Changes in PIP pre and post fall were compared using McNemars test with significance at $p < 0.05$.

Results: There were $n = 1{,}016$ patients eligible for analysis. The percentage of patients who had at least one STOPP criteria was 42.2% pre- and 42.9% post-fall ($X^2 = 0.19$, $p = 0.67$). When Beers criteria were applied the proportion of patients with at least one criteria pre-fall was 41.7% but did not change significantly post-fall 38.7%, $X^2 = 3.6$, $p = 0.06$). The most significant indicator to changed was long term (>4 weeks) use of benzodiazepines, which decreased from 10.7% to 8.6% ($X^2 = 8.1$, $p = 0.0045$).

Conclusions: There is a high prevalence of PIP in older patients presenting with a fall event to the ED. Positive changes in prescribing were seen in the area of benzodiazepines, but overall sustained improvements in PIP were not observed. Improved falls risk reduction has implications for healthcare policy development and could potentially be achieved by measures that prompt review of prescribing in at risk populations.

172. Abstract withdrawn by author.

173. Drug Use among Elderly People in China – A Pooled Study

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Background: Numerous studies have described the patterns of drug utilization in the elderly in the USA and Europe. However, despite the rapid increase of aging of its population in China, such data have not yet been summarized.

Objectives: To assess the patterns of drug use among the elderly in China.

Methods: Systematically reviewed the reports of drug use among people aged 60 years or older from 2000 and later in China. The pooled prevalence of common chronic disease and drug use was estimated.

Results: A total of 10,276 eligible subjects (4,880 males and 5,396 females) were extracted from 12 studies. The mean age was 72.5 years old. Eighty-five percent of the people dwelled in city communities. Eighty-two percent of the subjects had at least one chronic disease, with 28.70% having two conditions and 20.59% having at least 3 chronic conditions. Hypertension was the most common disease, followed by diabetes, coronary heart disease and osteoarthritis. Eighty percent of the elderly were taking at least one medication, Almost half of them taking three or more medications concurrently. Most commonly used prescription drugs were cardiovascular drugs, antidiabetics, and antibiotics. The proportions of use of Chinese traditional herbal medicine and some nourishments and food supplements also are reported. More than half of the people reported noncompliance. The reported rates of adverse drug reaction ranged from 2.06 to 10.90 percent.

Conclusions: Chronic diseases are very common among community-dwelling elderly people in China. A substantial proportion of elderly were consuming a high number of drugs and inappropriate drug uses are common.

174. Abstract withdrawn by author.

175. Bisphosphonate (BP) Route of Administration and Selected Health Outcomes of Interest (HOIs) among Women with Postmenopausal Osteoporosis (PMO)

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Background: Recent studies comparing the risk of fractures and other outcomes among oral and intravenous

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(IV) BP users have been equivocal, which may in part be due to the small number of IV relative to oral BP users. We set out to evaluate such associations within a large population.

Objectives: Among women with PMO, estimate incidence of selected HOIs (osteonecrosis of the jaw (ONJ), non-traumatic subtrochanteric/diaphyseal fractures, fracture healing complications, hypocalcemia, hospitalized infections, dermatologic events, pancreatitis, hypersensitivity, and primary malignancy) in those treated with IV and oral BP.

Methods: Within a PMO population derived from a US healthcare claims database, we defined osteoporosis medication exposure cohorts (BP, oral BP, IV BP, other osteoporosis medication, no osteoporosis treatment) from March 2005 through March 2010. HOIs were identified during eligible follow-up using claims-based algorithms. For each HOI, we estimated rate ratios (RRs) comparing the exposure cohorts for various risk periods (on-treatment only, on-treatment and post-treatment), overall and adjusted by baseline covariates.

Results: We identified 132,772 women aged ≥65 years with PMO, 54% of whom used BP upon cohort entry. Of the BP users, 98% used an oral BP. Overall, incidence estimates were similar across the varying exposure periods. Incidence of primary malignancy (RR and 95% confidence interval [CI]: 1.7 [1.2–2.3]) and hypersensitivity (RR: 2.7 [1.3–5.5]) were higher in the IV BP cohort as compared with the oral BP cohort. Incidence of ONJ (RR: 4.5 [0.9–23.5]) among IV BP users was also somewhat higher though some confidence intervals included one.

Conclusions: Among women with PMO, increased risk of hypersensitivity and primary malignancy may be associated with IV BP use relative to oral BP use. Incidence of ONJ may also be elevated among IV BP users. The effect of residual confounding cannot be ruled out.

176. Abstract withdrawn by author.

177. Antipsychotic Drug Use and the Risk of Venous Thromboembolism in Elderly Patients with Dementia

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Background: Antipsychotics have been associated with an elevated risk of venous thromboembolism (VTE). Although antipsychotics are widely prescribed to elderly patients with dementia, no previous study was performed explicitly in this population.

Objectives: To investigate the association between the use of antipsychotics and the risk of venous thromboembolism in elderly patients with dementia.

Methods: Based on data from the German Pharmacoepidemiological Research Database, a nested case-control study was conducted within a cohort of 72,591 patients with dementia aged at least 65 years between January 1, 2004 and December 31, 2007. Cases were patients with a hospitalization due to VTE. Up to four controls were matched to each case according to age, sex, health insurance and calendar time via risk-set sampling. Users of antipsychotics (Anatomical Therapeutic Chemical classification system: N05A) were classified into former or current users. In addition, all current users were categorized as prevalent or new users. For a further analysis, we distinguished between users of either conventional or atypical antipsychotics and concurrent users of both conventional and atypical agents. Multivariate conditional logistic regression was applied to calculate odds ratios (OR) for VTE in all user groups compared to non-users.

Results: The case-control-dataset comprised 1,028 VTE cases and 4,109 controls. An increased risk of VTE was found for current users (OR = 1.23 95% CI: 1.01–1.50), for new users (OR = 1.63 95% CI: 1.10–2.40) and for users of a combination of atypical and conventional antipsychotics (OR = 1.62 95% CI: 1.15–2.27). The risk of VTE was not elevated in former users, prevalent users, and users of either conventional or atypical antipsychotics.

Conclusions: The current use of antipsychotics in elderly patients with dementia was associated with an elevated risk of VTE, especially during the first 3 months of use and for concurrent users of conventional and atypical agents. Further studies with larger sample sizes are required to investigate the risk profile of individual agents and possible interactions in more detail.

178. How Representative Is the Medicare Part D Population?

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Background: In the US, Part A/B Medicare claims are a rich source of healthcare data on older Americans (65+). As of 2006, data on dispensed prescription drugs are also available but only for those beneficiaries enrolled in a Part D drug plan.

Objectives: To evaluate the extent to which those with Part D are representative of the Medicare population as a whole, and to assess the ability of sampling weights to address over or under-representation of specific subgroups.

Methods: In a population-based, 20% random sample of Medicare beneficiaries age 65+ years and enrolled in 2007, we characterized age, race, sex, and state of residence. For those with fee-for-service (FFS) Part A/B, we characterized the prevalence of 19 chronic conditions. For those with FFS drug coverage (Part D), we characterized the annual prevalence of any use of 24 classes of common

medications. We estimated sampling weights for the probability of having FFS Part A/B coverage among all beneficiaries and the probability of having FFS Part D coverage among those with FFS A/B, conditional on all available characteristics for the sample. Predicted probabilities were used to weight those with complete FFS A/B/D claims back to the full Medicare population.

Results: Of 6,441,124 beneficiaries in the 20% random sample, 4,543,150 (70.5%) had FFS A/B; of those, 2,073,878 (45.6%) also had FFS Part D. Compared to the total population, individuals with complete FFS A/B/D coverage were 6 months older and less likely to be male (34% vs. 42%). Compared to those with FFS A/B, those with FFS Part D were more likely to have heart failure (23.4% vs. 19.8%) and depression (12.7% vs. 10.2%). The mortality rate in 2008 was 21% higher (7.1% vs. 5.3%) among those with FFS A/B/D. After weighting, the samples were similar in terms of demographic characteristics, but mortality remained slightly elevated. Estimates of the association between prevalent use of each drug class and mortality were similar with and without weighting.

Conclusions: While Medicare beneficiaries with complete data for pharmacoepidemiologic research is not strictly representative of all Medicare enrollees, sampling weights can be estimated and applied to generate population-based prevalence estimates.

179. Altering Eligibility Criteria to Identify Disease Cohorts in Insurance Claims Databases: An Example of Postmenopausal Osteoporosis (PMO)

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Background: Women with PMO are often identified in insurance claims data by postmenopausal age, diagnosis of osteoporosis (OP) or osteoporotic fracture, and OP treatment. Because anti-resorptive medication is also indicated to treat cancer-induced bone disease, a look-back period of sufficient length is required to exclude cancer patients from PMO study cohorts.

Objectives: To evaluate how the sequence of PMO criteria and length of look-back period to exclude cancer patients impact identification of a PMO cohort.

Methods: Using MarketScan claims data, women ≥55 years old, enrolled in their health plan for ≥6 months (baseline), and with a diagnosis of OP or osteoporotic fracture or OP medication between January 2004 and July 2010 were included in Cohort I. Women were included in Cohort II only if they received an OP diagnosis or treatment after fulfilling age and enrollment criteria. Varying look-back periods were used to exclude patients with cancer diagnoses or treatment before cohort entry. Patient characteristics of both cohorts were described during the 6-month baseline.

Results: Cohort I was 10.3% larger than Cohort II (N = 1,555,572 vs. 1,395,931). Very minor differences in patient characteristics were seen between the two cohorts. Women in Cohort I tended to be identified by OP-related diagnosis (29.7% vs. 26.9%) rather than treatment, be <60 years old (31.2% vs. 29.9%), have <1 year of enrollment (64.7% vs. 59.9%), and have slightly more comorbidities and healthcare utilization but less use of medication during baseline than Cohort II. Relative to a 5-year look-back, using 3-year and 2-year look-backs included 4.4% and 9.4% more cancer patients in Cohort I and 4.6% and 7.7% in Cohort II, respectively.

Conclusions: Requiring OP diagnosis or treatment to occur after meeting age and enrollment criteria did not substantially affect the number and characteristics of identified women with PMO from an insurance claims database. Using shorter look-back periods to assess and exclude patients with cancer diagnoses or treatment may result in considerable misclassification of cancer patients.

180. Use of Medicines in a Rural Setting: Frequency of Subjects at Risk of Medicine Misuse

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Background: The ability of the elderly to use medicines in good conditions is important to limit the occurrence of adverse effects and to optimize drug benefit. Several physical disabilities or cognitive deficits may compromise adequate use of medicines, decrease the expected benefit and favor occurrence of adverse drug reactions.

Objectives: To estimate the proportion of subjects at risk of medicine misuse.

Methods: A cross-sectional pharmacoepidemiological study was conducted from baseline data collected in the AMI cohort, a French prospective cohort to study age-related pathologies that included 1,002 elderly subjects (65 years and older) living in rural areas and retired from agriculture. A standardized questionnaire was used at inclusion to collect socio-demographic characteristics, drug use, health status, social and medical context. For each subject, health care reimbursement data were extracted from the French health insurance database of the "Mutualité Sociale Agricole." We identified the frequency of subjects at-risk of medicine misuse through a classification considering, for each user, socio-demographic characteristics, social and medical context, and disability data. This frequency was assessed overall, and

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considering three cognitive statuses (dementia with clinical diagnosis, cognitive impairment not dementia [CIND], and no cognitive impairment).

Results: Overall, 3% of subjects were at risk of medicine misuse: this proportion was 2.6% in demented subjects, 4.2% in subjects with CIND, and 2.5% in subjects with normal cognitive status. In this rural population, the majority of subjects at risk of medicine misuse declared themselves autonomous for medication use but were visually impaired. Independently of visual impairment, the proportion of subjects at-risk would have been 0.3% overall, 0.2% in those demented, 0% in CIND, and 0.1% in normal subjects.

Conclusions: The great majority of subjects were not in a situation where they were at risk of drug misuse. Results suggest that better optical correction may considerably reduce the frequency of those at risk.

181. Significant Differences between Methods to Estimate Renal Function May Have Major Inplications in Drug Dosing and Adverse Reactions in the Elderly: Concordant Results in a Cross-Comparison between Croatia and Sweden

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Background: Decline in renal function in patients aged 65 years or older is assumed to be associated with increased risk of adverse drug reactions (ADRs). Glomerular filtration rate (GFR) estimation prior to initiation of therapy could therefore result in decreased ADRs-related morbidity in the elderly. However, differences between estimation formulas of renal function may contribute to the development of over- or under treatment. In general, dose recommendations are based on the Cockroft-Gault (CG) equation.

Objectives: To identify differences of GFR estimation formulas in elderly patients.

Methods: We compared two cohorts of elderly patients acutely admitted to two university hospitals in Sweden (N = 274) and Croatia (N = 450). GFR was estimated using CG with uncompensated creatinine, the abreviated MDRD4 (Modification of Renal Disease) equation and CKD-EPI equation based on compensated creatinine tracable to IDMS.

Results: Mean age, weight and S/P-creatinine for the Croatian patients were 75 ± 6 years, 74 ± 13 kg, and 122 ± 102 μmol/L, respectively, and for the Swedish patients 81 ± 8 years, 68 ± 16 kg, and 116 ± 62 μmol/L, respectively. Patients from Croatia showed significantly lower clearance with CG equation than both MDRD4 and CKD-EPI equations, 49 ± 21 mL/min, 64 ± 35 and 60 ± 27 mL/min/1.73 m^2, respectively ($p < 0.0001$). Patients from Sweden showed similar results: 39 ± 18 mL/min, 58 ± 27 and 55 ± 24 mL/min/1.73 m^2, respectively ($p < 0.0001$), even though the Swedish patients were significantly older and had lower weight compared to Croatian patients ($p < 0.001$).

Conclusions: MDRD4 and CKD-EPI showed significantly higher GFR than CG, irrespective of the country. The difference between the methods to estimate renal function may cause that greater doses are given to elderly patients, thus increase the risk for adverse drug reactions. For many drugs depending on renal elimination and with a narrow therapeutic index, this would have a major impact on the outcome in elderly.

182. Adverse Drug Reactions in Patients with Alzheimer's Disease or Another Dementia in France: A National Cross-Sectional Study

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Background: Alzheimer's disease (AD) and other dementia have been declared a French public health priority. Even though the adverse drug reactions (ADR) induced by acetylcholinesterase inhibitors and memantine are well known, and the drugs inducing memory loss clearly identified, the ADR occurring in patients with cognitive impairment are less well characterized while these patients often receive numerous medications.

Objectives: To assess the ADR occurring in patients with AD or other dementia in France.

Methods: A one-day cross sectional multicentre study was conducted (15/2/2010–15/5/2010) by the network of the 31 regional pharmacovigilance centres. The subjects were selected so as to make up a representative sample of the patients with AD or another dementia and of their dwelling in metropolitan France. After randomization, subjects were included from memory consultation units, acute-, intermediate- and long-care geriatric units, and nursing homes. Socio-demographic data, history, ADR and drugs given were registered.

Results: Of 1,332 subjects 82.0 ± 8.0 year-old (46–108) were included; 61.3% with AD. The mean number of drugs was 6.3 ± 3.1. Anti-dementia drugs were given to 66.4% subjects. The prevalence of ADR was 5.0% (95%

CI: 3.9–6.2) without a significant difference between at home and institutionalized patients. The most frequent ADR were related to the gastro-intestinal tract (23.2%) and the central nervous system (17.4%). 31.9% of the ADR were judged serious and 47.8% avoidable. The drugs most often involved were anti-dementia drugs (29.0%), cardiovascular drugs (29.0%) and psychotropic drugs (26.0%, anxiolytics, hypnotics, antidepressants, neuroleptics).

Conclusions: This study is the first survey conducted over the whole French territory demonstrating that the pattern of iatrogenesis in patients with dementia, whatever its cause, is similar to that expected in the general population. However, special attention is required when prescribing psychotropic and anti-dementia drugs, as they are frequently used and induce half of the ADR in this population.

183. Drop-Out Rates in Patients with and without Screening Period in the SCOT Trial

Li Wei,[1] Thomas M MacDonald,[1] on behalf of the SCOT study group collaborators.[2] *[1]Medicines Monitoring Unit, University of Dundee, Dundee, United Kingdom; [2]Research Institutions, Europe.*

Background: The Standard care vs. Celecoxib Outcome Trial (SCOT) is an ongoing large streamlined safety study comparing the cardiovascular safety of celecoxib therapy with traditional NSAID therapy in patients with osteoarthritis or rheumatoid arthritis and in the setting of the normal healthcare system in European. The trial stopped a 2 week screening period after September 2010 for new participants as many patients could not tolerate the screening period.

Objectives: To determine if the drop-out rate varied between patients with and without screening period.

Methods: The drop-out rates were calculated at 30 days, 90 days and 180 days. Chi-square test and logistic regression model were used to determine whether there was a statistically significant difference in drop-out rates between the two groups.

Results: Of 3,470 patients were randomised in the study between February 2008 and January 2011. Of 2,545 patients had a screening period before the randomisation and 925 did not. In total, 86 patients discontinued the study at the end of 180 days of follow up. The drop-out rates at 30 days, 90 days and 180 days were 0.1%, 1.1% and 2.1% (n = 1, 10, and 19) in the group without screening period and 0.2%, 0.9% and 2.6% (n = 6, 23, and 67) in the group with screening period (p = 0.46, 0.63 and 0.33; respectively). The adjusted odd ratio for drop-out was 1.28 (95% CI 0.76–2.14) for patients who had screening period at the end of 180 days of follow up. There were no differences in drop-out rates between patients in age, gender, high blood pressure, alcohol intake, smoking history, total cholesterol and co-morbidity of asthma and diabetes.

Conclusions: Removing screening period did not change the drop-out rate in the trial.

184. Variations in Recruitment Rate in a Multicentre Streamlined Safety Trial

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Background: Recruitment rates are low in clinical trials and existing strategies appear to have little impact on recruitment rates. There is no data on recruitment rates in large streamlined trials of drug safety. We are conducting a large streamlined safety study in patients with osteoarthritis or rheumatoid arthritis in the setting of the normal healthcare system in Europe. Prescription charges are reimbursed in Denmark and Netherlands but since all subjects were over 60 they are not incurred in the UK.

Objectives: To determine the recruitment rate in different centres.

Methods: Eligible patients were identified from the medical notes at participating practices in nine centres across the UK, Denmark and Netherlands. An invitation letter with study information and consent form was sent to each patient. The Recruitment rate was calculated as number of positive responses divided by number of letters sent out. Chi-square test was used to determine differences between centres.

Results: Of 22,205 patients were invited to take part in the study. The overall recruitment rate was 32.1%. The recruitment rates were 12.3% (252/2,057), 20.1% (1,080/5,376), 21.4% (53/248), 24.0% (346/1,439), 31.8% (1,941/6,102), 35.5% (83/234), 36.5% (724/1,983), 51.8% (1,304/2,515) and 60.0% (1,350/2,251) for each centre. The variation of recruitment was statistically significant between centres ($p < 0.01$).

Conclusions: Recruitment rate varied from very low (< 20%) to moderate (> 50%). Reasons why these variations exist require further exploration.

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185. Observational Cohort Study of Pneumonia in Enfuvirtide-Exposed and Unexposed Patients

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Background: This study was undertaken because of the observation in pre-approval clinical trials that HIV infected patients treated with enfuvirtide (FUZEON®) plus an Optimized Background (OB) of highly active antiretroviral therapy (HAART) appeared to have a higher incidence of pneumonia than patients on OB alone.

Objectives: To assess the frequency of pneumonia and 5 other endpoints (sepsis/bacteremia, bacterial sinusitis, serious skin infections, esophageal candidiasis, cytomegalovirus retinitis) developing in HIV-1 infected patients newly initiated on enfuvirtide in addition to HAART compared with patients on HAART not exposed to enfuvirtide.

Methods: A non-interventional Phase IV post-marketing multi-center observational cohort study was conducted at 110 US investigator sites (March 13, 2003 to August 14, 2008) with 740 enfuvirtide-exposed and 1,110 propensity score (PS) matched comparator patients. Patients, age >15 years with a CD_4+ cell count ≤ 400 cells/mm^3 at index, were observed until loss to follow-up, therapy switch, death, or study end date. Patient medical records were reviewed every 6 months to abstract endpoint data. An Adjudication Panel conducted blinded reviews of all endpoints.

Results: A total of 1,850 patients were observed for 5,546 patient-years, median 3.0 years. The exposed group had a higher proportion of males, and a higher proportion of Hispanic and Caucasians; CD_4 count and viral load were significantly lower and higher ($p < 0.001$), respectively, than in unexposed patients. The PS-adjusted risk ratio for pneumonia (confirmed or probable) in enfuvirtide-exposed patients, relative to unexposed patients, was 1.23 (95% CI: 0.86–1.60). The incidence of pneumonia was 3.2 events/100 patient-years in the enfuvirtide-exposed arm and 1.8 events/100 patient-years in the unexposed arm. The hazard ratio, adjusting for other baseline risk factors, was 1.34 (95% CI: 0.90–2.00).

Conclusions: The results showed no significant evidence of difference in risk of pneumonia or other selected endpoints, when comparisons were adjusted for the effects of unbalanced risk factors by the PS methodology, however, a significant increase in risk could not be ruled out.

186. Impact of Managed Problem Solving (MAPS) Antiretroviral Adherence Intervention on Depressive Symptoms

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Background: Managed Problem Solving (MAPS) is a five-step behavioral adherence intervention delivered by trained staff through 4 face-to-face and 9 telephone contacts over 3 months followed by monthly telephone "booster sessions." It targets depression as one of the potential adherence barriers, but its effects on depressive symptoms are unknown.

Objectives: We aimed to determine the effect of MAPS on depressive symptoms.

Methods: We conducted a secondary analysis of a randomized single-blind trial comparing MAPS with usual care (UC). Patients were: ≥18 years old, newly starting antiretroviral therapy (ART) or starting a new regimen after failing current ART with HIV RNA ≥1,000 copies/mL. All regimens included ≥3 drugs, at least 2 fully active. The outcome for this analysis was depressive symptoms measured quarterly using the CESD with an a priori defined cutoff of ≥22 for severe depressive symptoms. The effect of MAPS on severe depressive symptoms was compared to UC using logistic generalized estimating equations. Whether virologic success with ART mediated the effect of MAPS on depressive symptoms was tested by including viral load in the models and assessing changes in the point estimate of the relation between MAPS and depression.

Results: Of 91 were randomized to MAPS and 89 to UC. Median age was 42 years, with 61% male, 85% Black, median baseline viral load of 2,000 copies/mL, and median CD4 count of 250 cells/mm^3 with 41/180 (23%) having baseline CESD≥22. Characteristics were balanced between groups. MAPS was associated with substantially decreased likelihood of severe depressive symptoms over follow-up than usual care: OR = 0.45 (95% CI 0.21, 0.93). No confounders were identified and inclusion in the models of viral load at each time point had no effect on this association.

Conclusions: Although focused on adherence, the MAPS intervention also decreases severe depressive symptoms in a highly symptomatic HIV population. The effect of MAPS on depressive symptoms was not mediated by its effect on viral load. The added benefit of MAPS on depressive symptoms over and above its impact on adher-

ence and virologic outcome makes it even more appealing for widespread implementation.

187. Efficacy and Safety of Tenofovir for the Treatment of Chronic Hepatitis B: A Systematic Review

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Background: Chronic hepatitis B is a disease of high prevalence and are estimated 350 million cases worldwide.

Objectives: Systematic review of the efficacy and safety of tenofovir for the treatment of CHB in patients without HIV co-infection.

Methods: All studies of efficacy and safety with tenofovir were included, irrespective of blinding or language. The databases Medline, Lilacs, Central and NHS-Centre for Reviews and Dissemination were searched until December 2011. Target outcomes were virological, biochemical, and histological response, HBeAg seroconversion and adverse effects.

Results: The search identified 1,126 titles and the reviewers selected six. Tenofovir provided significant results for undetectable HBV DNA. In RCTs, Berg et al. (2010) demonstrated that 66% of patients achieved the outcome at 48 weeks. For the same period, 76% of HBeAg-positive patients and 93% of HBeAg-negative achieved the outcome in a study conducted by Marcellin et al. (2008). After 144 weeks, according to Heathcote et al. (2011), the outcome was achieved in 72% of HBeAg-positive patients and 87% of HBeAg-negative. In a retrospective study of van Bommel et al. (2006), 95% of patients achieved the outcome at 96 weeks. About biochemical response, 68% of HBeAg-positive patients and 76% of HBeAg-negative normalized ALT levels after 48 weeks. After 144 weeks, 58% of HBeAg-positive patients and 74% of HBeAg-negative achieved the outcome. Marcellin et al. (2008) demonstrated that there was histological response in 74% of HBeAg-positive patients and in 72% of HBeAg negative. HBeAg seroconversion was 21% at 48 weeks, 21% at 144 weeks and 24% at 70 weeks. No resistance was associated to tenofovir. Tenofovir was well tolerated, no serious adverse event occurred in more than one patient and no patient had signs of decompensated cirrhosis. There were no reports of death associated to tenofovir.

Conclusions: Despite the lack of studies evaluating tenofovir, the available clinical results shows high efficacy for the treatment of CHB and low rates of resistance. Thus, tenofovir is indicated for the treatment of CHB in adults without HIV co-infection. Further studies are needed to strengthen the evidence.

188. Incidence of Adverse Reactions in HIV and TB Co-Infection: A Prospective Study

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Background: The concurrent administration of ART and ATT is associated with increased risk of development of ADRs. High burden of HIV and TB co-infectionhis necessitates the need for large prospective studies related to drug toxicity.

Objectives: To assess the incidence, severity, predictability and preventability of ADRs and to identify the risk factors in HIV patients co-infected with TB for ADRs.

Methods: The study was conducted at two sites, an ART centre and a community care centre. The hospitalized HIV patients co-infected with TB were enrolled and reviewed for occurrence of ADRs. The causality of ADRs was assessed using WHO scale and Naranjo's Algorithm. The ADRs were coded using WHO adverse reaction terminology. The statistical analysis of data was done using Pearson Chi Square test and Fischer Exact test. Bivariate logistic regression was used to identify the risk factors for ADRs.

Results: Of 274 patients were followed in 352 consecutive patient episodes. The prevalence of ADRs was 70.7% (249). ADRs were the cause of hospital admission in 69 (27.7%) admission episodes whereas 180 (72.2%) ADRs were observed during the hospital stay. Amongst the observed ADRs, 239 (95.9%) ADRs were predictable, the causation of 140 (72.2%) ADRs were not preventable. The incidence of ADRs was higher in female patients (OR: 1.9; $p = 0.005$). Patients who did not have a history of TB and diagnosed for the first time are at 70% risk of experiencing ADRs. (OR: 0.5; $p = 0.04$). The patients who were on zidovudine based regimen along with ATT formed the major proportion of ADRs (66.26%, $p < 0.001$). Patients who were on stavudine based regimen are at 40% lower risk of experiencing drug related adverse event when compared to zidovudine [OR: 0.2 (CI: 0.1–0.5). The duration of hospital stay (5–10 days) [OR: 1.8 (CI: 1.2–2.9), total number of medications received (>10) [3.4 (CI: 1–15), were identified as a risk factor for ADRs.

Conclusions: HIV patients newly diagnosed with TB and patients on zidovudine based regimen should be monitored closely for ADRs. Seventy percent of HIV patients co infected with TB are at a higher risk of experiencing ADRs irrespective of their CD4 count.

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189. Hearing Impairment Associated with Oral Terbinafine Use

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Background: The Netherlands Pharmacovigilance Centre Lareb received six reports of hearing impairment in association with oral terbinafine use. This study describes these cases and provides support for this association from the Lareb database of spontaneous ADR reporting and from Vigibase, the adverse drug reaction database of the WHO Uppsala Monitoring Centre.

Objectives: The objective of the study is to identify whether the observed association between oral terbinafine use and hearing impairment, based on several cases received by Lareb, supports a safety signal.

Methods: Cases of hearing impairment in oral terbinafine users are described. In a case/non-case analysis, the strength of the association in Vigibase and the Lareb database was determined by calculating the reporting odds ratios (ROR), adjusted for possible confounding by age, sex and possibly ototoxic concomitant medication. RORs are calculated for deafness, hypoacusis, and the combination of both, defined as hearing impairment.

Results: In the Lareb database, six reports concerning individuals aged 31–82 years, who developed hearing impairment after starting oral terbinafine, are present. The use of oral terbinafine is disproportionally associated with hypoacusis in both the Lareb database (adjusted ROR = 3.9, 95% CI: 1.7–9.0), and in Vigibase (adjusted ROR = 1.7, 95% CI: 1.0–2.8). Deafness is not disproportionally present in either of the databases. The pharmacological action of terbinafine is based on the inhibition of squalene epoxidase, an enzyme present in both fungal and human cells. This inhibition might result in decreased cholesterol levels in, among others, the outer hair cells of the cochlea, possibly leading to impaired cochlear function and hearing impairment.

Conclusions: To our knowledge, hearing impairment associated with oral terbinafine use has not been described before. A causal relationship between the use of oral terbinafine and hearing impairment is possible, based on statistical analysis of reported cases in different databases and a possible pathophysiological explanation.

190. Safety Profile of Antiinfectives Used in a 13 Years Period, Report of a National Pharmacovigilance Centre

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Background: It is reported that antibiotics induced adverse events are responsible for an estimated 142,000 emergency department visits per year in the United States. Anti-bacterial agents are responsible for approximately 25% of adverse drug reactions in hospitalized patients. The incidence of antibiotics induced adverse events in hospitalized patients is estimated as 5%.

Objectives: To evaluate all registered cases of adverse events induced by antiinvectives in Iranian pharmacovigilance database. To detect preventive measures for reducing resulted complications.

Methods: All recorded adverse events in pharmacovigilance database from 1998 through 2011 were reviewed for those induced by antiinfectives. The extracted data were categorized based on factors related to patients, suspected medicines and adverse events. Assessment of system-organ classes, seriousness and causality of reactions was performed according to World Health Organization scale. Preventability of adverse events was analyzed based on Schumock questionnaire.

Results: Antiinfectives were the most reported drug class in reported adverse events. Among 29,356 registered adverse events, 8,054 (27.4%) were suspected to be induced by antiinfectives. There were 301 cases of death recorded in our database in which 127 cases were related to antiinfectives. The highest number of detected events was reported with ceftriaxone (2,574 cases). Ceftriaxone (82 cases) and Penicillin (20 cases) were the mostly reported medicines in fatal reactions. The route of administration in recorded fatal cases was mostly reported as intravenous and intramuscular. Anaphylactic reactions had the highest frequency of registered serious reactions. Inappropriate use of medicines was the most detected cause of preventability in evaluated data.

Conclusions: Antiinfectives can induce severe and life-threatening adverse events. The high frequency of serious reactions could be influenced by rapid intravenous injection, unlabeled use and previous patient history of allergic reactions to antibiotics.

191. Abstract withdrawn by author.

192. Characterization of a Cohort of Incident Hepatitis C Patients in the US (2005–2010): Comorbidities, Use of Medications and Diagnostic Tests

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Background: Chronic Hepatitis C (CHC) is a serious disease that can result in long-term illness.

Objectives: To describe characteristics of an incident cohort of patients with CHC in US, including prevalence of comorbidities and use of medications and diagnostic tests.

Methods: Data from the American Gastroenterological Association Digestive Health Outcomes Registry and the MedAssurant Medical Outcomes Research on Economics and Effectiveness Registry (2005–2010) were analyzed. Incident CHC cases were identified by: (1) ≥2 ICD-9-CM codes for CHC or ≥1 code for acute hepatitis C virus (HCV) infection with ≥1 code for CHC (first claim was designated the index date); (2) no prior HCV infection or treatment; (3) at least 12 months of continuous enrollment before and after index date; and (4) age ≥18 years. Pharmacy claims for peginterferon or ribavirin defined CHC treatment. Comorbidities, medications, and HCV diagnostic tests were identified by ICD-9-CM, NDC, and procedure codes.

Results: Of 32,194 patients met study criteria and had mean (SD) age 53 (±13) years, 52% male, and insurance source Medicaid for >50%. Mean (SD) follow-up was 27 (±12) months. Pre-existing comorbidities included: hypertension (35%), mental health disease (29%), diabetes (27%), coronary heart disease (16%), alcohol dependence (14%), drug dependence (14%), cirrhosis (8%), and heart failure (8%). Common medications pre-index date included calcium-channel blockers (15%), benzodiazepines (13%), statins (13%), and oral antihyperglycemics (12%). While 65% (n = 20,944) had evidence of anti-HCV antibody or RNA testing (qualitative or quantitative) in the 60-days prior to index date or any time thereafter, 48.3% (n = 15,564) had a quantitative RNA test. Overall, 9% (n = 2,845) had evidence of CHC treatment. Sixty-seven percent (n = 1,902) of treated patients had a quantitative RNA test after treatment initiation.

Conclusions: Among CHC (mostly Medicaid) patients, the prevalence of treated comorbidities was high, while few (9%) patients were treated for HCV. Findings suggest opportunities for quality improvement for use of diagnostic tests and treatment in this patient population.

193. Long-Term Effectiveness of Ribavirin Plus Pegylated Interferon Combination Therapy for Hepatitis C Patients in Taiwan: A Population-Based Study

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Background: Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, cirrhosis, and liver cancer worldwide and no vaccine is currently available to prevent infection. Ribavirin plus pegylated interferon is a standard therapy to eradicate HCV infection and result in sustained virologic response; however, data related to the long-term effects of this combination therapy are still limited.

Objectives: Evaluate the long-term effectiveness of ribavirin plus pegylated interferon combination therapy.

Methods: This retrospective longitudinal study obtained data from the Taiwan Cancer Registry, the National Health Insurance claims data, the treatment program for chronic hepatitis C, and death certification (2003–2009). Patients in the treatment group received combination therapy; patients in the control group received no treatment. Outcomes included the incidence of hepatocellular carcinoma (HCC) and survival rates. Cox proportional hazard model was used to control covariates, including age, sex, and comorbidity.

Results: Since 2003, when a program to reimburse hospitals for Hepatitis C treatment was launched, the number of patients receiving treatment has been increasing. After excluding patients with hepatitis B and alcoholic liver disease as well as those previously diagnosed with HCC, the treatment group included 38,087 patients. The incidence of HCC was significantly lower in the treatment group than in the control group (HR = 0.19, $p < 0.0001$), and the overall survival was significant increased (HR = 0.122, $p < 0.0001$).

Conclusions: Antiviral treatment using a combination of ribavirin plus pegylated interferon is effective to prevent hepatocellular carcinoma and improve the survival of patients with chronic hepatitis C.

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194. Oseltamivir Treatment and Adverse Outcomes and Influenza-Related Complications in Children and Adults

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Background: Questions have been raised about oseltamivir's safety and effectiveness for influenza.

Objectives: The objective of this retrospective cohort study was to assess adverse events following oseltamivir treatment for influenza.

Methods: Health insurance claims data from the Optum Normative Health Information (NHI) database from October 2007 through September 2009 were used to identify patients with a diagnosis of influenza (ICD = 9,487 or 488) associated with a physician visit or hospitalization. Patients with an oseltamivir dispensing on the day of influenza diagnosis and a dose/days supply consistent with treatment were compared to propensity-score matched patients who received no antiviral therapy for 7 days ± date of diagnosis. Outcome measures included incident claims for colitis, neuropsychiatric events, thrombocytopenia, hypothermia, skin hypersensitivity, bleeding, otitis media, pneumonia, and other respiratory complications. Risk ratios (RR) and 95% confidence intervals (CI) were calculated separately for ages <18 and ≥ 18.

Results: Each group included 26,081 patients. Patients <18 in the treatment group had significantly more incident claims for depressive disorder (RR 3.14, 95% CI 1.05–9.67). There were no significant increases in claims for adverse outcomes for adults receiving treatment. For treated youths, respiratory complications were reduced in the 3 main categories (otitis media RR 0.31, 95% CI 0.24–0.42; other respiratory RR 0.74, 95% CI 0.66–0.83; pneumonia RR 0.49, 95% CI 0.33–0.74). RRs for these complications in treated adults tended to show nonsignificant reductions.

Conclusions: Compared to no antiviral therapy, oseltamivir treatment of influenza in patients <18 years of age was associated with more claims for depressive disorder, and fewer claims for certain respiratory outcomes. Limitations of the study include its exploratory nature and inability to validate claims.

195. Risk of Acute Liver Injury in a Cohort of Oral Antimicrobial Users

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Background: Many antimicrobials (AMs) are associated with acute liver injury (ALI), but few large, population-based studies have been reported.

Objectives: Estimate relative risks of hospitalization or emergency visit for ALI with use of 8 AMs (amoxicillin, amoxicillin/clavulanic acid, clarithromycin, cefuroxime, doxycycline, levofloxacin, moxifloxacin, telithromycin) compared with nonuse.

Methods: Our study population was drawn from the HealthCore Integrated Research Database[SM], 2001–2009. We excluded patients with infectious hepatitis, HIV/AIDS, chronic alcoholic liver disease, or pregnancy. The case definition was based on international consensus criteria (Benichou C. J Hepatol 1990;11:272–6). Case screening and source record validation (blind to exposure) were described previously (Kaye JA, et al. PDS 2011;20:S5). To control for confounding, we conducted a nested case-control analysis (NCCA) (10 controls per case, matched on age, sex, and event date).

Results: Among 1.3 million AM users, we identified 607 cases of ALI (295 uncertain and 312 validated [VALI] cases, including 63 that were "idiopathic" [ID]), 82 cases of severe hepatocellular injury (SHI), and 11 cases of liver failure (LF). ALI incidence per 10^5 person-years (95% CI) was 35 (29–42) during nonuse and 235 (165–324) during current use of multiple AMs (CMU). In the NCCA, adjusted odds ratios (AORs) (95% CI) for CMU were 2.5 (1.5–4.2) for ALI, 3.2 (1.6–6.7) for VALI, 10.9 (2.0–60.5) for ID, and 12.3 (2.8–53.0) for SHI. Levofloxacin had the highest AOR for current single use (CSU) in most analyses: ALI 1.8 (1.2–2.8); VALI 3.2 (1.8–5.8); ID 3.5 (1.1–10.6); SHI 7.2 (2.1–25.2). Also elevated were respective CSU AORs for moxifloxacin—1.3 (0.8–2.2), 2.3 (1.1–4.7), 2.9 (0.8–10.4), 3.1 (0.6–17.3); amoxicillin—1.5 (0.9–2.6), 2.3 (1.1–4.7), 3.7 (1.1–12.7), 6.9 (1.9–25.6); and amoxicillin/clavulanic acid—1.5 (0.9–2.6), 2.5 (1.3–5.0), 4.0 (1.2–13.1), 6.0 (1.4–25.7).

Conclusions: We saw modest elevations in adjusted rate ratios for some AMs (estimated as AORs), but we observed little evidence of any strong effect of commonly used AMs on ALI. However, we did find a comparatively

high adjusted rate ratio among patients exposed concurrently to multiple AMs.

196. Abstract withdrawn by author.

197. Sepsis Antibacterials as Marker for Sepsis Incidence in a Clinical Database?

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Background: Sepsis is an important medical condition in patients in the intensive care unit (ICU) that is associated with high mortality. Its clinical diagnosis is challenging. Identification of patients with sepsis is a key validation step for research in electronic ICU records that are mainly kept for clinical care.

Objectives: To assess specific antibacterial drugs for treatment of severe infections as a criterion to identify sepsis cases.

Methods: We analyzed the electronic medical records from the 26-bed surgical ICU of a tertiary care hospital from 2006 to 2011. We searched ICD10-GM code labels and free text entries for identification of patients with sepsis and compared these with patients whose prescription records indicated exposure to carbapenems, ureidopenicillins, levofloxacin, and ceftriaxone and metronidazole in combination, which are primarily used for sepsis therapy in our intensive care unit.

Results: We assessed 11,611 patients with 13,821 ICU admissions. Sepsis was identified in 2,065 admissions (14.9%) based on antibacterials, 1,029 admissions (7.4%) based on ICD code labels, and in 960 (6.9%) with both ICD code labels and free text entries. Only 745 (sensitivity 77.6%) of the latter received specific antibacterials, i.e., sepsis was not recorded in 63.9% of admissions with this exposure. Specificity of supposedly sepsis specific antibacterials was 89.7% with the same reference group.

Conclusions: In our clinical database local standard antibacterials for sepsis are more often prescribed to patients having no recorded sepsis than those with this sepsis indicator. A significant proportion of patients with a record of sepsis does not receive any of these drugs, indicating that both markers on their own may not be sufficient to identify the full spectrum of cases. As exemplified by sepsis, reliable detection of complex conditions may require more intricate algorithms in clinical databases.

198. Use of Antimalarial Chemoprophylaxis and the Risk of Developing Eye Disorders

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Background: Malaria is an important cause of serious illness in travellers returning from endemic regions. Ocular toxicity has already been described in the late 1950s for some antimalarial drugs but only limited information is available on the association between malaria chemoprophylaxis and ocular toxicity.

Objectives: This study aimed to assess the risk of developing a first-time diagnosis of any eye disorder associated with the use of mefloquine (M), chloroquine and/or proguanil (CP) or atovaquone/proguanil (AP) for malaria chemoprophylaxis and to compare it to a comparison group of patients not exposed to anti-malarial drugs.

Methods: We used the UK General Practice Research Database to conduct a follow-up study with a nested case-control analysis for the period 2001–2009. Conditional logistic regression analyses were used to estimate the odds ratio of developing a first-time eye disorder in relation to use of a malaria chemoprophylaxis.

Results: The incidence rates of all eye disorders combined in users of M, CP or AP or travellers not using antimalarials were 5.3 (95% confidence interval (CI) 4.3–6.5), 7.1 (95% CI 5.0–9.9), 6.3 (95% CI 5.6–7.2) and 5.1 (95% CI 4.6–5.7) per 1,000 person years, respectively. As compared to non-users of antimalarials, the adjusted odds ratio in the nested case-control analysis for users of M, CP or AP were 1.33 (95% CI 1.01–1.75), 1.61 (95% CI 1.06–2.45), and 1.25 (95% CI 1.03–1.52), respectively. Results for individual ocular diagnoses will be provided.

Conclusions: The risk of eye disorders in users of mefloquine chemoprophylaxis was not higher than in users of other antimalarials. The data suggest that the use of antimalarials, in general might be associated with an increased risk of eye disorders.

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199. Epidemiology of Herpes Zoster and Its Complication: A Population Based Study in Israel

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Background: Herpes Zoster (HZ), is a predominantly dermal and neurologic disorder caused by the re-activation of a latent varicella-zoster virus (VZV) infection. The most common complication of HZ is persistent pain, also called postherpetic neuralgia (PHN), which may last for several months to years. Currently, vaccination against HZ is not universally administered in Israel.

Objectives: (1) To assess the incidence of HZ and of PHN in 2006–2010 in the general population of a large HMO in Israel and specifically in immune-compromised individuals, and, (2) to evaluate associations between risk factors and the probability of developing HZ and PHN.

Methods: A retrospective cohort database research

Setting: The study was conducted utilizing the longitudinal database of Maccabi Health Services, a 2 million member health maintenance organization operating in Israel (25% of the total population).

Main outcome measures: Cases of HZ and of PHN were identified for the period of 2006–2010 through a search for *International Classification of Diseases*, 9th revision codes. Other variables included age, sex, and socioeconomic status, and co-morbid conditions. Users of corticosteroids, immunesuppressants, chemotherapy, or radiotherapy were defined as immune-compromised patients.

Statistical analysis: Odds ratios and 95% confidence intervals were calculated for associations between risk factors and HZ and PHN.

Results: During the study period there were 30,327 and 1,705 cases of HZ and PHN, respectively. Incidence of HZ and PHN increased sharply with age. Among the elderly HZ cases, 13.9% and 4.6% developed PHN and ophthalmic complications, respectively. The incidence of HZ in immune-compromised patients was 11.4/1,000, and 17.0% of the elderly patients in this group developed PHN. In addition to age, the odds ratio for HZ and PHN was significantly higher in females, and patients with a history of cancer, diabetes mellitus, or transplantation.

Conclusions: Herpes zoster carries significant morbidity in Israel, particularly among the elderly and immunocompromised patients. Health policy makers should consider adopting the anti-HZ vaccine that may reduce the burden of this relatively widespread disease.

200. Risk of Venous Thromboembolism (VTE) in Patients with Chronic Hepatitis C (CHC)

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Background: Recent studies have suggested that patients with liver disease are at increased risk for VTE.

Objectives: Our aim was to determine the incidence and risk factors for VTE in the CHC population.

Methods: A cohort of CHC patients was developed in a US claims database. Patients with at least 2 ICD-9 diagnosis codes for CHC within 6 months of each other were identified from 2000 to 2009 (prior to the availability of direct-acting antiviral therapies for CHC). All CHC patients were included in the analyses regardless of treatment status. A comparison general population cohort (GPC) of non-HCV infected patients matched on age and gender to the CHC cohort was also developed. The outcome of incident VTE was defined as an ICD-9 code for VTE and an anticoagulant prescription within 90 days of the VTE diagnosis. Person-years at risk (PY) for each subject accrued from the index HCV diagnosis date. Incidence rate ratios (IRR) and 95% confidence intervals (CI) were calculated to describe the relative incidence among cohorts. A sub analysis assessed if VTE incidence differed among cirrhotic vs. non cirrhotic CHC patients.

Results: The analyses identified 47,391 CHC patients of which 68% were 45–64 years of age, 61% were male, 22% (10.288) were treated and 78% (37.103) were untreated. There were 50,291 patients in the matched GPC. The incidence of VTE in the GPC population was 2.27/1000 PY vs. 3.13/1000 in the CHC population (IRR = 1.38, 95% CI 1.11–1.72). The incidence of VTE in the non cirrhotic CHC group was 2.60/1000 PY vs. 3.67/1000 PY in the cirrhotic CHC group (IRR = 1.41, 95% CI 1.05–1.91).

Conclusions: This analysis indicated that HCV infection was associated with an increased risk of VTE. In addition, VTE risk was also increased among cirrhotics. There were limitations to the study as there was no adjustment for possible confounders such as comorbidities (e.g., cancer, liver transplant etc) known to increase the risk for VTE and the outcome of VTE was not based on medical chart review. Further analysis to assess mechanisms for the increased risk of VTE in specific CHC subgroups may be warranted.

201. Comparison of the Renal Safety of Tenofovir and Stavudine in Patients on Antiretroviral Therapy at a Kenyan Referral Hospital

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Background: Tenofovir (as disoproxil fumarate, TDF) is a nucleotide reverse transcriptase inhibitor that may be a safer alternative to stavudine (D4T) – and zidovudine-based first-line regimens for the treatment of HIV infection. Though current guidelines recommend TDF as first-line HAART, it causes severe renal adverse events. Its renal toxicity has never been compared to that of D4T in Kenyan populations.

Objectives: To compare the incidence and identify risk factors for nephrotoxicity in patients on stavudine and tenofovir-based HAART regimens.

Methods: The design was a three-arm comparative retrospective cohort study carried out at a HIV/AIDS clinic at a referral hospital in Kenya. The three arms included patients on any TDF-based, D4T-based regimens and other regimens. The study population was HIV-infected adults seen between January 2008 to March 2010. Data was abstracted from the medical records of 396 patients. Nephrotoxicity was defined as creatinine clearance <60 mL/min. The key covariates for nephrotoxicity were identified by Cox regression modeling. Data was analysed using SPSS (version 12.0) statistical software.

Results: The incidence rate (IR) of nephrotoxicity was higher in patients initiated on TDF than in patients initiated on low dose D4T (9.0 [95% CI: 5.0–15.0] vs. 4.0 [95% CI: 2.0–7.0] cases per 1000 person-months respectively). The main risk factors for nephrotoxicity were: age >40 years (Adjusted HR = 2.88; 95% CI: 1.56–5.34; $p = 0.001$), weight <65 kg (AHR = 5.04; 95% CI: 2.06–12.32; $p < 0.001$), efavirenz non-nucleoside (AHR = 2.47; 95% CI: 1.24–4.94; $p = 0.010$) and concurrent amphotericin B (AHR = 20.68; 95% CI: 4.05–105.70; $p < 0.001$).

Conclusions: The incidence of nephrotoxicity in patients receiving TDF-based regimens is higher than patients on D4T-based regimens. The strong association between efavirenz and nephrotoxicity requires further investigation.

202. Antimicrobial Utilization for Culture-Confirmed Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections in a Large, Regional Cohort

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Background: MRSA control and prevention activities have received considerable research attention over the past 10 years, yet gaps in knowledge pertaining to treatment practices remain.

Objectives: To describe antimicrobial treatment regimens, including multi-therapy approaches, for culture-confirmed MRSA infections using a novel database we created of clinical microbiology culture and susceptibility results from 5 acute care facilities of the Veterans Affairs New England Healthcare System.

Methods: Patients with MRSA infections were identified from clinical cultures collected during hospital admissions between January 2004 and October 2010. Using pharmacy data, treatment regimens with anti-MRSA antimicrobials were assessed: clindamycin (CLN), daptomycin (DAP), doxycycline (DOX), linezolid (LZD), minocycline (MIN), rifampin (RIF), tetracyclines (TET), tigecycline (TIG), trimethoprim/sulfamethoxazole (TMP-SMX), and vancomycin (VAN). All antimicrobial combinations were evaluated in a 12-day exposure window: 1 day prior to the first positive MRSA culture collected during the admission plus the 11 days after.

Results: We identified 2,428 hospitalizations with exposures to anti-MRSA antibiotics. The most common culture sites were respiratory (34.3%) and skin (34.0%). Utilization was highest for VAN (77.5%), TMP-SMX (22.5%), and LZD (15.3%). Variations in utilization were observed by culture site. We observed the following monotherapy rates for each specific antimicrobial exposure: CLN 34.3% (71/207), DAP 17.5% (10/57), DOX 35.6% (37/104), LZD 29.1% (108/371), MIN 83.3% (5/6), RIF 7.9% (5/63), TET 58.3% (7/12), TIG 28.6% (2/7), TMP-SMX 44.7% (244/546), VAN 64.9% (1,220/1,881). Common overlapping exposures included VAN + TMP-SMX (9.1%) and VAN + LZD (7.6%).

Conclusions: We observed low rates of antimicrobial monotherapy for the treatment of culture-confirmed MRSA, highlighting an important research challenge in infectious disease pharmacoepidemiology. Quantifying

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antibiotic treatment patterns must account for short-term exposures with empiric therapy, switching to targeted therapies based on culture results, and combination regimens.

203. Antiretroviral Prescription and Adherence in a Portuguese Cohort of HIV-1 Infected Subjects: An overall Analysis of Changes over the Years 2005–2008

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Background: Knowledge on which Highly Active Antiretroviral Therapy (HAART) is used on HIV infection may provide useful information for clinical evaluation with regard to safety and effectiveness.

Objectives: To evaluate the trends in adherence to HAART in a cohort of HIV-1 infected adults, and to characterize the HAART prescription pattern over the period 2005–2008.

Methods: Retrospective cohort study, with a random sample of HIV-1 adult infected subjects, from the total of 2,861 subjects followed-up at a Portuguese hospital HIV outpatient clinic presenting at least one HAART refill between 01-01-2005 and 31-12-2008. Medication possession ratio (MPR) was determined using a fixed 12- or 6-month period. Non-adherence was defined as MPR < 95%. HAART prescription was analyzed according to regimens, within each antiretroviral class, and regarding fixed-dose combinations. Clinical characterization, including viral load (VL) and CD4 cell count, was retrieved from clinical records. The χ^2 test for linear trend was used to assess temporal differences within each variable, for a 5% significance level.

Results: From a total of 186 included subjects, 78.5% were treatment-experienced at baseline. Over the period 2005–2008, there was a significant increase in the proportion of non-adherent subjects, from 12.3% in 2005 to 25.9% in 2008 ($p = 0.03$). The proportion of subjects with at least one registry of detectable VL had significantly decreased from 43.5% in the first semester of 2005 to 29.2% in the second semester of 2008 ($p = 0.01$). The two most usual HAART regimens were two NRTIs and a NNRTI or a PI. The use of fixed-dose combinations had significantly increased from 54.8 to 77.7% ($p < 0.001$), mainly due to emtricitabine/tenofovir association.

Conclusions: Non-adherence increased over the period 2005–2008, but a better control of virological and immunological outcomes was observed. The prescription pattern seemed to be in accordance with guidelines for the HIV treatment, including the use of fixed-dose combinations.

204. Implications for Failure to Adjust Dose in Obese Patients: Higher Risk of Treatment Failure

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Background: Obesity is a health epidemic and that has been shown to compromise immune response increasing risk of infections. In addition, antibiotics can have altered drug disposition profile in obese patients affecting the attainment of therapeutic targets. If dose is not adjusted to account for this, obese patients may be at higher risk for antibiotic treatment failure (ATF).

Objectives: To determine is obesity is associated with ATF and if dose is weight adjusted in adults.

Methods: In a historical cohort study design, data were selected on 18,014 patients completing the 1992 and 1998 Santé Quebec Health surveys who consented to link with administrative health data. Eligible patients were 20–79 years old and dispensed at least one oral antibiotic between the survey date and December 2005. ATF was defined as a secondary antibiotic prescription or hospitalizations for infection within 30 days following initial therapy. Obesity was defined using BMI with a correction for self-reporting. Antibiotic daily dose (DD) and daily dose to body mass index (DD:BMI) ratios were estimated. Logistic regression was used to estimate the impact of obesity and dosing (e.g., DD:BMI) on ATF. One-way ANOVA with Tukey-Kramer adjustment for multiple comparisons was used to determine if DD:BMI ratios differed significantly across weight groups, reflecting a lack of weight-based dosing.

Results: Of the 6,179 patients selected, 828 (13.4%) had an ATF during the outcome assessment period. Obesity was found to be a significant predictor of ATF (OR 1.26; 95% CI 1.03–1.52), after adjusting for other potential confounders including sociodemographic and antibiotic-related factors (e.g., MRSA, history of antibiotic use). The antibiotic DD:BMI ratio means differed significantly between weight groups, where means decreased with increasing BMI. When included in the ATF predictive model along with other confounders, the DD:BMI variable was significant (p-value 0.03).

Conclusions: We found that obesity was a significant predictor of ATF after controlling for other risk factors. This association is likely due to the lack of variation in the dose. This has important health implications for obese patients.

205. Antibacterial Use: Age and Gender Specific Prescribing

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Background: In Hungary the prescription database do not directly linked to patient's age and gender, which limits the assessment of patient characteristics in drug utilization studies.

Objectives: To assess characteristics of age and gender specific antibiotic use in a Hungarian region (Southern Great Plain region – SGP region).

Methods: A descriptive study was performed in 20 retail pharmacies of the region (total number of pharmacies in SGP = 445). Each pharmacy was personally visited and manual review of dispensed prescriptions was performed. The study was conducted between January and June, 2007. From each month, 6 workdays per pharmacy were included in the analysis. The study days were selected by double permutation method to provide diversity in days and months. Prescriptions pertaining to antibacterials (ATC: J01) were identified. The product name, the dispensed quantity, the gender and age of the patients were recorded. Patients were classified as children if under the age of 14 years, adults between 14 and 65 years of age and as elderly above 65 years of age.

Results: Overall around 50,000 prescriptions were dispensed in the 20 pharmacies during the 120 study days, of which 2,811 referred to antibiotics. In total 1,006 prescriptions were indicated for children, a 1,494 for adults and 311 for the elderly. In adult patients we detected a female dominance (63.4%) while in the children group a slight boy dominance was found (53.4%). In both gender and in every age group the amoxicillin and clavulanic acid combination (co-amoxiclav) was the most frequently prescribed agent. In children in the top three most frequently used agents were also amoxicillin, cefuroxime, in adults clarithromycin, clindamycin, while in the elderly ciprofloxacin and norfloxacin, respectively. Stratifying by genders, four out of the top five agents were identical.

Conclusions: The present study confirmed that children are responsible for more than one-third of antibiotic therapies. Although the most frequently prescribed antibiotic was uniformly the co-amoxiclav, the most popular antibiotics differed between age groups but not between genders.

206. Antibiotic Consumption in 8 European Countries: Analyses from Data Provided by IMS Health

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Background: High out- and inpatient antibiotic (AB) consumption and an increasing resistance due to mis- and overuse of ABs warrant monitoring of AB consumption from an economic and health-related perspective.

Objectives: We descrbe the frequency of use of macrolides (J01FA) and amoxicillin/clavulanic acid (J01CR02) in the out- and inpatient sectors of 8 countries.

Methods: Data from the MIDAS database was extracted for the years 2007–2009. An ATC code was assigned and defined daily doses/1,000 inhabitants/day (DID) were calculated, for the in- and outpatient health sector of France (FR), Germany (DE), Italy (IT), Netherlands (NL), Norway (NO), Poland (PL), Spain (ES), and United Kingdom (UK). J01FA and J01CR02 were chosen as they have been associated with a higher risk of drug-induced hepatotoxicity.

Results: In 2009, total J01FA consumption ranged between 2.39 DID (DE) and 5.45 DID (IT), and the total J01CR02 use was 0.70 DID (DE) and 11.87 DID (ES). Over the 3-year period, the J01FA consumption increased slightly in FR, DE, IT, and UK; J01CR02 increased in all countries except for ES. In both healthcare sectors, the differences in ABs use were mainly seen at the most detailed ATC level 5. Insert *Outpatient*: J01CR02 (38.58 DID), clarithromycin (10.38 DID), azithromycin (5.63 DID), and erythromycin (2.90 DID) were the most frequently used agents in 2009. Insert *By country*: ES, UK, and IT ranked highest in the use of the four above mentioned ABs. Insert *Inpatient*: J01CR02 (3.56 DID), clarithromycin (0.62 DID), azithromycin (0.23 DID), and erythromycin (0.25 DID) were the most commonly used agents in 2009. Insert *By country*: FR consumed most J01CR02, whereas J01FA were most used in the UK.

Conclusions: The application of the ATC/DDD methodology in the context of in- and outpatient DU allows for comparisons of the two healthcare settings and across countries.

The major consumption of J01FA and J01CR02 is in the outpatient sector. Not having information on total group (J01) does not allow to know the relative consumption of subgroups J01FA and J01CR02.

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207. Ongoing Programmes to Reduce the High Rate of Antibiotic Consumption in Serbia; Current Situation and Future Direction

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Background: Currently high antibiotic consumption in Serbia. Patients have been able to purchase antibiotics directly at community pharmacies, which is illegal – now changing with growing recognition of the need to reduce inappropriate antibiotic consumption.

Objectives: (1) Assess the extent of self purchases in Serbia; (2) Compare overall antibiotic consumption with other EU countries; (3) Suggest measures to reduce antibiotic consumption.

Methods: Retrospective drug utilisation analysis of antibiotic consumption (DDD/TID) including the Penicillins (J01CA, J01CE, J01CF, J01CG, J01CR), Cephalosporins, Macrolides and Quinolones in both databases: reimbursed/prescription (RZZO – Health Insurance database) and total including self purchases (Medicines and Devices Agency – ALIMS database) from 2005 to 2009. Total utilisation in 2007 compared with ESAC database (http://www.esac.ua.ac.be/main.aspx?c=*ESAC2 and n = 50026). Of 2007 chosen as midpoint between years.

Results: (1) Reimbursed antibiotic use decreased in Serbia by 5% (16.74 DDD/TID in 2005 vs. 15.94 DDD/TID in 2009). (2) Total antibiotic use (ALIMS data) increased overall utilization of antibiotics in Serbia – 38.21 DDDs/TID in 2005 (128% increase vs. RZZO) and 34.35 in 2009 (115% increase vs. RZZO). (3) Lowest% change in total consumption in 2009 vs. 2005 (DDD/TID) was – 2.5% for the penicillins vs. 27% increase for cephalosporins and quinolones; (4) Serbia – third highest utilization for cephalosporins, highest for penicillins, second highest for macrolides, and third highest for quinolones vs. EU in 2007.

Conclusions: Self purchasing of antibiotics in Serbia high increasing overall utilisation by 115% to 128% (ALIMS vs. RZZO databases). Reducing antibiotic consumption must become a high priority among all national authorities to reduce resistance development and conserve resources – already happening with greater enforcement of the law regarding self purchasing and instigation of prescribing restrictions for second line antibiotics. Quality indicators will shortly be introduced building on those suggested by ESAC and locally adapted ones. Their influence will be assessed and reported in the future.

208. Patterns in Influenza Antiviral Medication Use before and during the 2009 H1N1 Pandemic, Vaccine Safety Datalink Project, United States, 2000–2010

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Background: U.S. recommendations for using influenza antiviral medications changed in response to viral resistance and during the 2009 H1N1 pandemic. Little information is available on corresponding changes in use, including clinician adherence to recommendations to reduce adamantane use and to focus on protecting high-risk patients.

Objectives: To characterize population-based outpatient influenza antiviral medication usage, including diagnosis and testing practices. To identify factors associated with oseltamivir dispensings during the 2009 H1N1 pandemic compared with pre-pandemic influenza seasons.

Methods: Eight medical care organizations in the Vaccine Safety Datalink Project provided data on influenza antiviral medication dispensings from January 2000 through June 2010. Dispensing rates were explored in relation to changes in recommendations and influenza diagnosis and laboratory testing frequencies. Factors associated with oseltamivir dispensings in pandemic vs. pre-pandemic periods were identified using multivariable logistic regression.

Results: Antiviral use changed coincident with recommendations to avoid adamantanes in 2006, to use alternatives to oseltamivir in 2008, and to use oseltamivir during the pandemic. Of 38,019 oseltamivir dispensings during the pandemic, 31% were to patients not assigned an influenza diagnosis, and 97% were to patients not tested for influenza. Oseltamivir was more likely to be dispensed in pandemic vs. pre-pandemic periods to patients < 25 years-old

and to those with underlying conditions, including chronic pulmonary disease or pregnancy (all $p < 0.0001$).

Conclusions: Antiviral medication usage patterns suggest that clinicians followed recommendations to change antiviral prescribing based on resistance and to focus on high-risk patients during the pandemic. Medications were commonly dispensed to patients without influenza diagnoses and tests, suggesting that antiviral dispensings may offer useful supplemental data for monitoring influenza incidence.

209. The Effect of Reimbursement System vs. Global Financial System on Prescribing and Cost of Antibiotics

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Background: There are few data on antibiotic prescribing within Indonesian hospitals. There is concern that antibiotics are costly in hospitals.

Objectives: Our objectives were to compare generic prescribing, total cost, and cost of commonly prescribed antibiotics in reimbursement system vs. global financial system.

Methods:

Design: A cross sectional study.

Setting: Prescription of 162,441 and 13,137 outpatients was obtained retrospectively from the medical record at the private hospital in East Kalimantan, Indonesia, from January 2006 until June 2006 (reimbursement system) and from July 2008 until December 2008 (global financial system).

Exposures or interventions: Reimbursement system vs. global financial system.

Main outcome measures: Percentage of generic antibiotics, antibiotics cost per patient, commonly prescribed of antibiotics.

Statistical analysis: t-test, analysis of variance and Chi square test.

Results: Total usage antibiotics was 8.8% (n = 14,214). Compared with reimbursement system, antibiotics usage was significantly decreased in global financial system (55.8–44.2%). Use of generic antibiotics was significantly increased (36.7–63.3%). Total cost of antibiotics spent per patient was significantly decreased (IDR 94,708.60–52,294.95). Cost spent per patient for amoxicillin (IDR 48,853.76–26,518.95), cefixime (IDR 153,983.20–105,194.73), cefadroxil (IDR 88,766.68–66,204.95) and ciprofloxacin (IDR 114,052.86–26,378.54) were significantly decreased. Percentage use of amoxicillin (44.85–35.48%) prescribed was decreased. Percentage use of cefixim (7.84–20.10%), cefadroxil (7.96–8.17%) and ciprofloxacin (4.52–6.93%) prescribed were increased. Percentage of branded antibiotics was significantly higher in reimbursement system (RR 1.16, 95% CI 1.135–1.190, $p < 0001$).

Conclusions: Compared with reimbursement system, cost of antibiotics was decreased on global financial system. The risk to write branded antibiotics was higher in reimbursement system.

210. Treatment of Acute Cystitis in Hungary: Quality of Antibiotic Prescribing

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Background: Cystitis is one of the main indication of antibiotic use in the ambulatory care. The ESAC team recently worked out and published disease-specific quality indicators which enable to assess the quality of antibiotic use in frequent infections.

Objectives: To reveal the general treatment patterns of cystitis in Hungary and to assess the findings in relation to the ESAC developed quality indicators.

Methods: Antibiotic use data was purchased from the National Health Fund Administration. The study period was between 2007 January and June. All antibacterial prescriptions claimed in Hungarian retail pharmacies during this half year were included in the analysis. Antibiotic use was evaluated by means of the ATC/DDD methodology (version 2008). The registered ICD (International Classification of Diseases version 10) codes enable us to evaluate antibiotic use by indication. Quality indicators of antibiotic prescribing proposed by the ESAC (usage rate of recommended antibacterials and usage rate of quinolones) were determined.

Results: For cystitis we registered 1.13 DDD per 1,000 inhabitant-days (DID) antibiotic use (6.30% of all systemic antibacterial use). The top three agents used in cystitis were: norfloxacin (0.31 DID, 25.2%); ciprofloxacin (0.23 DID, 18.6%) and sulfamethoxazol-trimethoprim combination (0.17 DID, 13.8%). The cumulative share of the ESAC recommended antibacterial agents in cystitis (J01XE; J01EA; and J01XX ATC groups) were used only in 22.87% compared to the recommended range of 80–100%. Meanwhile, the cumulative use of fluoroquinolones were 54.77%, which is well above the ESAC recommended acceptable range (0–5%).

Conclusions: In relation to the ESAC developed quality indicators, the treatment of cystitis in Hungary is far from

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optimal. Comparison to national guideline is warranted before drawing final conclusion on quality of antibiotic use.

211. Prescribed Dosages and Dosage Forms of Antibacterial Treatment

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Background: The ambulatory consumption of antibacterials is often studied only at an aggregated level and when in-depth analysis is made most frequently the patient characteristics is in the focus. Characteristic of the drug therapy such as the prescribed dosage and administration route is rarelly explored.

Objectives: To reveal the characteristics of antibacterial therapies mainly focusing on prescribed dosages and dosage forms.

Methods: The study was performed in 20 retail pharmacies of the Southern Great Plain region (total number of pharmacies = 445). Each pharmacy was personally visited and manual review of dispensed prescriptions was performed. The study was conducted between January and June, 2007. From each month, 6 workdays per pharmacy were included in the analysis. Study days were selected by double permutation method to provide diversity in days and months. Systemic antibacterial (ATC: J01) prescriptions were identified. The official product name, the dispensed quantity, the prescribed dose (only in adults) and dosage form were recorded. Patients were classified as children if under the age of 14 years and as adults above 14 years of age.

Results: Out of the 50,000 redeemed prescriptions 2,849 referred to antibiotics. Patients were treated by antibacterial monotherapies almost exclusively (2,813 cases). Parenteral treatment was used rarely (in 20 cases). Within oral antibacterial products, the average share of liquid oral forms was 11.5% and these forms were prescribed for children in every but five case. In more than 90% of cases one package of antibacterial was prescribed on one prescription. The prescribed daily dose were in good accordance with the WHO defined DDDs in most cases. Only amoxicillin (1.89 ± 0.57 vs. 1 g, oral co-amoxiclav (1.44 ± 0.39 vs. 1 g) and cefuroxime (0.83 ± 0.25 vs. 0.5 g) tended to be dosed higher than the WHO average maintanance dose.

Conclusions: Oral monotherapy with one package of antibacterial is the standard treatment in the Hungarian ambulatory care. The prescribed doses of only three antibacterials exceed significantly the WHO defined DDD.

212. Antibiotic Use across Five European Countries: A Drug Utilization Study from the ARITMO Project

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Background: The objective of the ARITMO project is to analyze the ventricular arrhythmogenic potential 400+ non-antiarrhythmic drugs. Rough estimates indicate that around 5% of persons are treated with antipsychotics each year, 30% with anti-infectives and 10% with antihistamines. However, several studies have highlighted relevant differences in prescribing patterns in Europe, which might affect the power to detect safety signals over the wide range of drugs under study.

Objectives: To describe the use of antibiotics in adults across 5 different European countries.

Methods: Descriptive study using General Practice (Health Search, CSD LPD; THIN) and record linkage databases (Emilia Romagna Database (ERD); PHARMO; Aarhus; GEPARD) with a target population of around 27 million patients from EU. Population level analyses has been performed using prevalence of drug use and DDD/1,000 inhabitants per day as key prescribing indicators. Person level analyses were conducted in order to evaluate mean patients exposure over study period.

Results: A seasonal trend was observed in all countries with peaks observed in winter. Total antibiotic consumption did not significantly differ across the countries. Conversely, the pattern of prescription appeared significantly different, with beta-lactamase resistant penicillins (i.e., phenoxymethylpenicillin) mostly prescribed in Denmark (Aarhus: 230/1,000 PY), whereas penicillins with extended spectrum mostly used in Italy (HSD and ERD), Netherlands (PHARMO) and in the UK (THIN). Fluoroquinolones were more prescribed in Italy (ERD: 102.9/1,000 PY; HSD: 88.9/1,000 PY) and Germany (GEPARD: 89.5/1,000 PY), compared to Netherlands (27.1/1,000 PY) or

UK (39.3/1,000 PY). Overall, when single medications were considered a wide variability across the countries was observed.

Conclusions: Results from this study confirm the variability in antibiotic use across the European countries. Reimbursment policies and national guidelines might explain the results. From the ARITMO perspective such results will help to select the drugs with enough power to assess the arrhythmogenic risk and to explore how cross-country variability might explain potential differences in risk.

213. Antimycotic Use across Europe: A Drug Utilization Study from the ARITMO Project

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Background: The arrhythmogenic potential of some antimycotics is documented by pre-clinical and clinical evidence. Within the ARITMO project (which investigates the proarrhythmic risk of antiinfectives, antipsychotics and antihistamines), we address differences in drug utilization among countries, since these may impact on the overall risk at the population level.

Objectives: To describe utilization of antymicotics across 5 different European countries.

Methods: Data on antimycotic use were retrieved from General Practice (Health Search, CSD LPD; THIN) and record linkage databases (Emilia Romagna Database; PHARMO; Aarhus; GEPARD) with a target population of around 27 million individuals from EU. Different Countries were compared in terms of antimycotic prescription rates per 1,000 person years (PY), DDD per thousand inhabitants per day (DID), distribution by age and by single agents.

Results: The prevalence of use resulted highest in Denmark (up to 27 per 1,000 PY in some months of 2008) and lowest in Germany (under 8 per 1,000 PY in any considered month). Concerning DID, Denmark, England and Netherlands can be considered high users (0.3–0.9 DID), whereas Germany and Italy low users (0.1–0.25 DID). In all countries, the highest prevalence of use was shown in the age range 20–44. The most prescribed agents were: fluconazole in Denmark and Italy, clotrimazole in Germany and England, gynaecologic miconazole in The Netherlands.

Conclusions: There are wide differences in the use of antimycotics among the 5 European countries. These differences impact on the reliability of analytical studies on proarrhythmic potential of a given agent. Once the proarrhythmic potential of a drug is known, collection of data on antimycotic consumption also in other countries will be useful to indirectly assess proarrhythmic risk by antimycotics at a population level. The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n 241679 – the ARITMO project.

214. Oseltamivir Utilization during the 2009 H1N1 Influenza Pandemic, Taiwan

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Background: A global pandemic of novel influenza A/H1N1 emerged from Mexico and US in March 2009. Antiviral medications are recommended to treat suspected or confirmed influenza patients, especially in those with high risk for morbidity and mortality. Influenza rapid test and oseltamivir were paid by National Health Insurance (NHI) and widely used during the influenza pandemic in Taiwan. The trends of prescription in specific age group and geographic difference are of particular interest.

Objectives: The aim of this study is to analyze the use of influenza virus antigen rapid test and oseltamivir during the 2009 H1N1 infleunza pandemic in Taiwan.

Methods: The study collected all influenza rapid test and oseltamivir prescription from NHI claims database in 2009. Rates of oseltamivir prescription in different age groups and regions are calculated using population data from Taiwan Statistical Yearbook of Interior. The trend of prescription was compared with measures of influenza virus activity from Taiwan Centers for Disease Control.

Results: There were 1,559,233 influenza rapid test conducted and 516,772 courses of oseltamivir prescriptions from NHI claims database in 2009. Less than 0.1% of oseltamivir were prescribed before August. Both peaks of oseltamivir and rapid test prescriptions were seen in week

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48, which were compatible with the trend of influenza virus activity. School-aged children had the highest oseltamivir prescription rate, followed by adolescents and preschool-aged children. The prescription rate in Taipei region peaked in week 44, which is earlier than other regions. Generally, oseltamivir prescription rate is low in southern Taiwan. Despite the mass oseltamivir treatment, the frequency of oseltamivir-resistant 2009 H1N1 influenza viruses in Taiwan was comparable to other countries.

Conclusions: The trends of influenza rapid test and oseltamivir prescription were closely related to the level of influenza virus activity. Oseltamivir prescription rate is high among persons aged under 18 years, who are at high risk of 2009 H1N1 influenza infection.

215. Pharmacoepidemiological Overview of Antimicrobial Prescribing Using a Large Claims Database in South Africa

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Background: Resistance to antimicrobial drugs is increasingly being reported in the medical literature in South Africa. It is important to know the general antimicrobial prescribing pattern and how this compares to other countries.

Objectives: To determine the general prescribing patterns of antimicrobial drugs to primary care patients in South Africa whose prescription was dispensed by community pharmacies.

Methods: A retrospective, cross-sectional pharmacoepidemiological study was conducted on prescription data of a national community pharmacy group in South Africa for 2010.

Results: A total of 660,500 patients received 1,576,593 antimicrobial products during 2010. The average age of patients was 34.23 years (females 35.21 years; males 32.86 years). Patients between 40 and 49 years received the highest average number of antimicrobial products (3.22). Nearly 60% of patients were females (58.32%), and they were prescribed 60.12% of antimicrobial products. Beta-lactams were the most often prescribed class (36.02% of antimicrobial prescriptions), followed by antiviral agents (20.92%) and quinolones (11.12%). Differences were observed between females and males with respect to the prescribing frequency of the different antimicrobial classes (χ^2 = 12,456; d.f. = 11; $p < 0.0001$), especially between anti-fungal agents and beta-lactam antibiotics. Within the beta-lactam class, penicillins accounted for 77.43% and cephalosporins for 22.49% of prescribing. Overall, the most often prescribed trade name product was a generic combination product of amoxicillin and clavulanic acid. The average cost per antimicrobial product was R121.70 (SD = R158.21). Anti-viral agents were the most expensive (R195.67), followed by aminoglycosides (R188.42). The average cost per over-the-counter product was R32.75, compared to R158.21 for prescription-only antimicrobials. ICD-10 Codes were used, but were not specific. There was a clear peak in prescribing during the winter months of the year (May to August).

Conclusions: This study provides an overview of antimicrobial prescribing to set the basis for comparative studies with other population groups, African countries and for more specific investigations.

216. Anti-Fungal Products Dispensed by a Group of Community Pharmacies in South Africa

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Background: There is increasing evidence of *Candida* species becoming resistant to some antifungal agents. It is therefore important to examine the current prescribing trends of antifungal agents in primary care.

Objectives: To determine the prescribing patterns of antifungal products over 1 year as dispensed by a large South African community pharmacy group.

Methods: A retrospective, cross-sectional drug utilization study was conducted on prescription data of a national community pharmacy group in South Africa for 2010. A total of 1,576,593 antimicrobial products were prescribed, of which anti-fungal products constituted 7.42%.

Results: A total of 84,912 patients received 116,955 antifungal products during 2010. (Average 1.38; SD = 1.05). Most products dispensed were not repeat prescriptions (84.98%). Diagnosis codes were not specific (mostly ICD-10 codes Z and U) and no seasonal trends in prescribing could be detected. The majority (70.86%) were prescription-only products (Schedule 4). Fluconazole was the most frequently prescribed active ingredient (42.14%), followed by nystatin (28.83%) and itraconazole (15.33%). The average age of patients was 37.64 (SD = 18.29) years with patients between 20 and 49 years receiving 49.44% of the products. Female patients were prescribed more anti-fungal products (69.67%) than antimicrobials (58.32%). In the age group under 16 years, nystatin (53.07%) and griseofulvin (26.74%) were the most frequently dispensed. In the age group 65 years and older, fluconazole (44.26%) and nystatin (27.27%) were the most often dispensed. The average cost per anti-fungal product was R123.19. Voriconazole products (22 prescriptions) were the most expensive (average of R8536.64). Nystatin-based products (mostly oral drops or oral suspensions) were on average the least expensive (R39.13 per product). In general, most anti-fungal products were capsules (55.38%), followed by oral drops (22.34%).

Conclusions: Fluconazole remained the most popular anti-fungal agent in primary care in South Africa. The need for diagnosis in databases is of critical importance to determine the cost of treating different types of fungal infections.

217. A Systematic Review of the Use of Antimicrobial Therapy for Symptom Management in Patients Receiving Palliative Care

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Background: The efficacy of antimicrobial therapy for symptom management in patients receiving palliative care is unclear.

Objectives: To systematically review studies evaluating the efficacy of antimicrobial agents for symptom management in patients receiving palliative care.

Methods: We queried the National Library of Medicine database for English-language original research articles published between 1/1/2001 and 6/30/2011 using the search terms: (palliative care OR terminal care OR hospice care OR end-of-life) AND (infection OR antibiotic OR antifungal OR anti-infective). Articles were included if the authors measured symptom response following antimicrobial therapy among patients receiving palliative care.

Results: Of 977 articles screened, 10 studies (all cohort studies) met inclusion criteria. Most studies (8/10) included patients in hospice programs or inpatient palliative care units. Measurement of symptom response varied from physician observation to the Edmonton Symptom Assessment Scale. Symptom improvement following antimicrobial therapy ranged from 15% (18/119) to 57% (359/633) of cases. Two studies included only parenteral antibiotic use and reported improvement in 47% (9/19) and 62% (27/43) of cases. Three studies reported symptom response by infection site with improvement in 79% (210/633) to 88% (14/43) of urinary tract infection cases and 38% (96/633) to 55% (6/43) of respiratory tract infection cases; 2 of these studies reported no improvement in bacteremia cases (3 and 25 cases). Two studies reported fever resolution in 48% (47/119) and 54% (43/93) of antimicrobial-treated cases, with one study reporting resolution in 7% (1/14) of cases not treated with antimicrobials.

Conclusions: Limited data exist regarding the efficacy of antimicrobials for symptom relief in patients receiving palliative care. Pre/post measurements suggest that symptoms often improve while on antimicrobial therapy, however a lack of controlled studies and variability in patient populations and symptom measures limit the validity of the data. Additional research is needed to guide antimicrobial use in the palliative care setting.

218. Multidisciplinar Interventions to Improve Antibiotic Use

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Background: The spread of antibiotic resistance in developing countries is associated to unnecessary prescribing antibiotics and increasing of self-medication.

Objectives: To carry out a critical review about the effectiveness of educational interventions in the population and health professionals, to improve antibiotic use and costs associated, in primary care and hospital setting.

Methods: Systematic search of studies published from January of 2001 to December 2010 on Pubmed, about educational interventions involving health professionals (pharmacists and/or physicians) and patients or their caregivers and/or general population to improve antibiotic use.

Results: Twenty two articles presented criteria for inclusion and were selected. Interventions were targeted at physicians and patients or their caregivers (or general population) and in two studies interventions included also pharmacists. Educational interventions in health professionals included dissemination of printed/audiovisual educational materials, group education, feedback of physician prescribing patterns, and, patients education included pamphlets and videotapes and, interventions in general population included divulgation by media. In most studies results of interventions were positive for all outcomes measured.

Conclusions: Interventions to improve antibiotic use should include improvement of prescription and dispensing habits.

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219. Factors Related to Antibiotic Resistances – How Could Community Pharmacists Improve It?

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Background: Antibiotic resistance has been related to inappropriate use, and pharmacists are in an ideal position to promote appropriate antibiotic use through patient education because of their direct access to the general population.

Objectives: To identify pharmacists' knowledge and perceptions about antibiotic resistances.

Methods: A qualitative research in the form of focus groups (FG), Study was developed, from December 2010 to April 2011, in an area of Statistically Territorial Unity Nomenclature (NUT) II of Portugal, defined by Health Northern Regional Administration (ARS-N), which includes five geographical districts and Focus Groups were conducted with 4–7 pharmacists, by a moderator using a constructed top guide. Participants were informed about the study and that sessions were audio-recorded, and signed an informed consent and ARS-N was informed about this study.

Results: A total of six focus groups were conducted (n = 32). Pharmacists identified four factors as principle causes of resistances: (1) self-medication with leftovers from previous treatment, and/or acquisition of antibiotics in some pharmacies without prescription, (2) patients' no-compliance of dosages prescribed; (3) excess/inadequate antibiotic prescription by physicians; and (4) an excessive use of antibiotics in consumption animals, without respect to withdrawal periods. Pharmacists suggested some interventions to modified this factors and improve antibiotic use: periodic determination of resistances in the community, regulatory measures to avoid prescription of new molecules, divulgation of new antibiotic resistances, and hospital studies to primary care health professionals, more interaction between pharmacists and physicians in pharmacotherapy decision, and between primary care and hospital, more control on dispensing of antibiotics without prescription, more information and awareness about the impact of taking antibiotics for animals, educational interventions on health professionals and on population.

Conclusions: Some interviewed pharmacists have the perception of their important role in the fighting against antibiotic resistance.

220. Healthcare Utilization in Phase 3 Telaprevir Clinical Trials for the Treatment of Genotype 1 Chronic Hepatitis C Patients

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Background: Telaprevir (INCIVEK™) is a hepatitis C virus protease inhibitor indicated in combination with peginterferon and ribavirin (PR), for treatment of genotype 1 chronic hepatitis C (CHC) in adult patients.

Objectives: To compare frequency of visits to all healthcare providers other than the trial investigators among patients treated with telaprevir (TVR) or placebo (PBO) with PR.

Methods: Two phase 3 randomized placebo-controlled trials comparing TVR to PBO were analyzed. ADVANCE enrolled treatment-naive CHC patients and REALIZE enrolled CHC patients who failed prior PR therapy. Patients in ADVANCE were randomized to TVR for 12 weeks with PR for 24 or 48 weeks (TPR) or PBO with PR for 48 weeks (PPR). REALIZE patients were randomized to TVR for 12 weeks with PR for 48 weeks (TPR) or PPR.(NEJM 2011;364:2417) Outpatient visits to providers other than clinical trial investigators were collected. Proportion of patients with ≥1 visit and mean and median number of visits per patient were calculated. Type of specialty visited was analyzed.

Results: In ADVANCE, 195 (53.7%) of 363 TPR patients and 173 (47.9%) of 361 PPR patients had visits. Mean (95% CI) number of visits per enrolled patient was 1.9 (1.4–2.4) and 1.7 (1.3–2.1) for TPR and PPR, respectively. Among patients with visits, mean (95% CI) number of visits was 3.6 (2.7–4.5) and 3.6 (2.8–4.4); median (range) was 2 (1–54) and 2 (1–52) for TPR and PPR, respectively. In REALIZE, 176 (66.2%) of 266 TPR subjects and 73 (55.3%) of 132 PPR patients had visits. Mean (95% CI) number of visits per enrolled patient was 3.5 (2.9–4.1) and 2.8 (1.3–4.3) for TPR and PPR, respectively. Among patients with visits, mean (95% CI) number of visits was 5.3 (4.4–6.1) and 5.1 (2.5–7.7); median (range) was 3 (1–35) and 2 (1–93) for TPR and PPR, respectively. More than 10% of patients in both trials visited specialties of primary care, dermatology, ophthalmology, radiology, emergency, dentistry, and psychiatry.

Conclusions: In post-hoc analyses of clinical trials, no differences were observed among patients treated with TVR

or PBO with PR in the frequency of visits to healthcare specialties other than trial investigators.

221. Antimalarial Drug Utilization and Parasite Density among Patients in a Nigerian Teaching Hospital

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Background: Prompt treatment is the mainstay of malaria control. ACTs are the recommended first line drugs. Home management of malaria strategy recognizes the importance of and seeks to improve the effectiveness of self medication practices.

Objectives: To determine the prevalence and pattern of drug utilization among patient with presumptive diagnosis of malaria.

Methods: A retrospective study among patients presenting for qualitative and quantitative microscopic examination of blood film for malaria parasite between January and December 2010.

Results: Three thousand four hundred and thirty seven patients aged 24.1 ± 20.9 years, with female preponderance, 59.2% were studied. Two-thirds (66.1%) of the patients used 1–3 drugs singly or in combinations. Of the 2,869 drugs utilized, analgesics, 47.3%; antimalaria, 38.9%,included coartem,10.6%,artesunate,10.8%, sulphadoxine-pyrimethamine,6.0%, amodiaquine,4.0%, chloroquine,3.3%,other antimalarias,4.1%; antibiotics,5.1% and other drugs,8.4%. ACTs used as fixed combination therapy or otherwise in 20%. Blood films for malaria parasites were negative in most patients. Parasite density was 6,185 ± 24,553, range 10–345,600; less than one-third of parasitaemic patients had heavy parasitaemia; in children, under 5 years 22.2%, other children 61.1%, and adults 16.7%. Parasite density correlated negatively with age r = -0.139, p = 0.000; was significantly higher in children. Drug use, at least three in number was most common among non-parasitaemic patients, reduced to two in number and progressively decreased in frequency from scanty through moderate parasitaemia. However, a high frequency of drug use was also seen among the heavy parasitaemic patients. Coartem was the most frequently used antimalarial drug among non-parasitaemic patients and was used by a heavily parasitized patient. Amodiaquine was not used by any of the heavy parasitaemic patients.

Conclusions: Conclusion: Prompt treatment of malaria promoted by HMM or self medication may be helpful in controlling malaria but severity in those who have malaria in spite of drug use is a menace to contend with. This may not be unrelated to doubtful rational use of drug and risk of drug resistance.

222. Determinants of Antibiotics Presciption among Doctors in a Nigerian Teaching Hospital

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Background: The problem of antimicrobial drug resistance is highly prevalent in many parts of the world with overwhelming magnitude in the resource poor nations like Nigeria. Irrational uses of currently available agents are major contributory factors. These includes irrational prescribing, dispensing and utilization by end users. An understanding of the factors influencing antibiotics prescription among doctors becomes necessary to be able to plan appropriate intervention strategies.

Objectives: The study aimed at identifying the factors influencing the choices of antibiotics prescription among the doctors at the Lagos State University Teaching Hospital, Nigeria.

Methods: This was a cross sectional survey of the determinants of antibiotics prescription among doctors in the Lagos State University Teaching Hospital, Ikeja, Through a structured questionnaire, information was obtained about the doctors and factors determining their uses of antibiotics. Statistical tests were carried out with SPSS 15.0; continuous variables were expressed as means (standard deviation), categorical variables as proportions.

Results: Of 98 respondents were studied with mean age of 36.24 (9.01) years, mean duration of practice of 10.68 (9.25) years, males, 64.3%. Respondents cuts across all clinical subspecialties. About 97% prescribe antibiotics frequently, mostly based on clinical judgments (93.9%) and experiences (87.8%) with rare laboratory supports. No evidence for existence of institutional policies regarding antimicrobial therapies. Factors of cost, drug availability and information from pharmaceutical representatives evidently influences drug uses.

Conclusions: There is an urgent need to institute measures to promote rational antimicrobial uses in the studied population.

223. Prevalence and Susceptibility Patterns of Urine Isolates of *Escherichia coli* to Various Fluoroquinolones in South-South Nigeria

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Background: Bacterial resistance to antibiotics is one of the reasons for treatment failure. In developing countries, were there is inadequate staffing and laboratory facilities,

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empiric treatment is normally used. Information on antimicrobial susceptibility patterns are scarce in these resource poor settings.

Objectives: To determine prevalence of *E. coli* as an aetiologic agent in urinary tract infections infections and its antimicrobial susceptibility patterns to different fluoroquinolones as a guide for empiric therapy in Nigeria.

Methods: A retrospective study was carried out using two clinical microbiology laboratories in South-South Nigeria. Data retrieved from medical records included number of *E. coli* isolates and antimicrobial susceptibility to ciprofloxacin, ofloxacin, levofloxacin and nalidixic acid (fluoroquinolones) popularly used in the country for the treatment of bacterial infections, between 2005 and 2009. The data collected was analysed using SPSS version 14 (Chicago, IL, USA) to determine prevalence patterns of *E. coli* and levels of resistance of the isolates to the four fluoroquinolones used.

Results: There were a total of 3,655 urinary isolates, *E. coli* accounted for 52.24% (1,909) of the isolates. Susceptibility to ofloxacin, ciprofloxacin, levofloxacin and nalidixic acid is 56.6%, 53.5%, 50.3% and 36.6%.

Conclusions: Despite the high level of resistance, there was continued use of these antibiotics in the empiric treatment of urinary tract infections. It is important, that there should be continuous monitoring/surveillance of antimicrobial susceptibility in order to encourage judicious use of antibiotics so as to minimize emergence of drug resistant bacteria. Development of a hospital antibiogram is a necessity in individual settings.

224. Outpatient Antibiotic Prescription in the South of Portugal

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Background: Antibiotic abuse and misuse are recognized as important determinants for bacterial antibiotic resistance. Although there are frequent calls to stop the unnecessary use of antibiotics, both consumption and resistance are escalating over the world.

In the last decade (2000–2009) was observed in Portugal a considerable decrease in antibiotic consumption (-8.65% DHD) but in the southern region (Algarve) this decrease was much lower (-2.63%), being relevant to study antibiotics standard use in this region.

Objectives: In order to assess the antibiotic pattern use and its determinants in Algarve, an epidemiological study was undertaken aiming to characterize antibiotic prescription for different infectious diseases in Primary Care.

Methods: A Drug Use Study (Prescription-Indication Study) was performed in a convenience sample of 60 General Practitioners (GPs) working in Algarve region. Each GP collected information about therapeutic, clinical and socio-demographic profiles of the last 20 patients who were prescribed with one or more antibiotics for systemic use. The statistical analysis was performed using SPSS (v17).

Results: About 95% (57/60) of the invited GPs sent the requested data. A total of 925 patients were included in the study, 40% of them were male. The mean age of the patients was 41.4 years (range: 0 and 94; SD = 24.14), with 63.3% <40 years. These patients were prescribed 943 antibiotic drugs for different infectious conditions. The most common were respiratory (50.5%) and urinary tract infections (29.8%). Penicillins were the antibiotic group most prescribed (43.7%), followed by macrolides (20.2%) and quinolones (19.3%). Amoxicillin-clavulamic acid (21.3%), amoxicillin (13.9%), ciprofloxacin (13.5%), azitromicin (10.0%) and clarithromycin (8.7%) were the antibiotic molecules (ATC – level 5) more frequently prescribed. Penicillins (49.0%) and macrolides (35.1%) were more frequently prescribed in respiratory infections, while quinolones (51.0%) and penicillins (16.1%) were the most common in urinary infections.

Conclusions: The information obtained in this study can be used to analyze the pattern of antibiotic prescribing in Algarve to promote better use of these medicines.

225. The Effect of Depression Risk in HIV Patients on Anti-Retroviral Therapy (ART) Choice and the Risk of Subsequent Depression Diagnosis after Exposure

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Background: Depression is common among HIV patients. The purpose of this study was to determine if depression risk affects actual clinical practice.

Objectives: The objective was to determine if background depression risk is related to the initiation of efavirenz and if efavirenz exposure is related to subsequent depression diagnosis.

Methods: Patients with ≥2 HIV diagnoses (ICD9-CM 042), and ≥18 years old were identified from the Thompson-Reuters MarketScan Commercial Claims and Encounters database (Q1/2004–Q3/2010). Following the earliest HIV diagnosis date, each efavirenz exposed patient was matched to 5 patients with non-efavirenz ART exposure. Logistic regression was performed predict-

ing efavirenz use. Demographic variables, depression diagnoses, depression-related comorbidity (Arteriosclerosis, diabetes, coronary artery disease, hypertension, peripheral vascular disease, cancer, stroke, opportunistic infections) and conditions (pregnancy, substance abuse) in the 12 months prior were independent variables. Logistic regression was used to examine the risk of depression diagnosis post-efavirenz exposure controlling for differences at baseline.

Results: Of 234,668 HIV patients met inclusion criteria, 8,635 of which had a history of depression. Compared to non-efavirenz therapy, patients receiving efavirenz had less history of depression (OR = 0.21, CI = 0.19–0.23), pregnancies (OR = 0.10, CI = 0.08–0.13), alcohol abuse (OR = 0.29, CI = 0.25–0.33), depression-related comorbidities (OR = 0.81, CI = 0.80–0.83), and female gender (OR = 0.49, CI = 0.47–0.50) prior to exposure. Patients exposed to efavirenz in 2006 (longest follow-up in dataset) had an increased risk (OR = 1.31, CI = 1.16–1.48) of subsequent depression diagnosis compared to non-efavirenz ART. Analyses with shorter follow-up were not significant.

Conclusions: There appears to be significant channeling of efavirenz away from patients who have depression or risks related to depression. Despite this effect, there remains a small increased risk of depression in patients treated with efavirenz compared to other ARTs. Depression is an important consideration to ART selection for HIV patients.

226. From Indication to Time in Therapeutic Range. Effectiveness of Oral Anticoagulation Guidelines in Patients with Atrial Fibrillation

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Background: Oral Anticoagulation is highly recommended in patients with atrial fibrillation (AF) for its efficacy in preventing stroke. Data on OAC global effectiveness (i.e., from prescription rate to time spent in therapeutic range – TTR) in a cohort of patients with AF discharged from hospital are lacking.

Objectives: We aimed at assessing the effectiveness of stroke prevention guidelines in a cohort of patients discharged with non valvular atrial fibrillation from the 2 hospitals of Agency for Health Services no. 3"Upper Friuli."

Methods: All patients discharged by hospitals with non-valvular AF diagnose during year 2009 were enrolled in this study. Record linkage in the previous 5 years and pharmaceutics data were used to assess comorbid conditions (ICD9-CM) and to calculate CHADS score. Prescription was obtained by discharge letters. Patience adherence to OAC prescription was assessed through administrative pharmacies data, and prothrombin/international normalized ratio (INR) from the whole "Upper Friuli" laboratories for a period of 180 days after discharge. A patient was considered to purchase OAC if at least one drug purchase was found in the administrative pharmacies data. TTR was calculated in patients who had at least two INR measurements.

Results: Among the 509 patients (mean age 80 ± 8 years) with AF discharged (90% from internal medicine) from "Upper Friuli" hospitals in year 2009 (out of 10,844 patients discharged), 201 patients (39.5%) receive OAC prescription, but only 146 patients (28.7%) took OAC drugs. No correlation was found between OAC prescription and CHADS score grade (p = 0.36). Under prescription was not related to contraindication. Median TTR was 55.5% (87.3 days), mean TTR was 56.8% (88.7 days).

Conclusions: In hospital, OAC prescription in AF patients is very low and not explained by present or past comorbid condition. A second dropout is represented by patients low compliance. Third, in real life TTR levels are much lower compared to controlled trial on OAC treatment. Overall, OAC guidelines effectiveness in AF is very scarce and not entirely improvable with new anticoagulant classes.

227. Use of Oral Antiplatelet Agents in Friuli Venezia Giulia, Italy, 2001 to 2010: A Population-Based Study

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Background: In several countries including Italy, the use of oral antiplatelet agents (APAs) increased over the last decade. Indications for APAs include several conditions that require lowering the risk of arterial thrombosis, and often involve elderly patients. Use is associated to an increased risk of bleeding.

Objectives: To describe the use of APAs in the general population of the Italian region Friuli Venezia Giulia (FVG), approximately 1.2 million, from 2001 to 2010.

Methods: This population-based study used the FVG Health Services Databases (Dbs). All subjects prescribed

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APAs during 2001–2010 were identified in the Outpatient Prescription Db by ATC code B01AC. Residence in FVG was defined through record linkage with the Patients Identification Db. Annual and age- specific prevalence was calculated.

Results: Overall 251,862 residents, 50.9% men, received 4,767,760 prescriptions for APAs. From 2001 to 2010 the annual number of users increased by 38.8%, from 73,430 to 119,932, and the number of prescriptions by 50.3%, from 146,771 to 301,413. The APAs most commonly dispensed were: aspirin, 229,895 users (91.3%) and 4.021.986 prescriptions (average 17 per user), ticlopidine, 20,131 users (8.0%) and 677.714 prescriptions (average 33 per user). Clopidogrel was dispensed to 1,610 (0.6%) residents, with 61.532 prescriptions (average 38 per user). Most users (54%) were from 60 to 80 years of age at the first prescription, and 23.3% were above 80. The prevalence of APAs use increased from to 6.2% to 9.7% over the study period. In residents below age 50 the prevalence was 6.8% and increased with each age category up to 50.3% in age category 70–79. In the elderly above 80, the prevalence was 46.3%.

Conclusions: The prevalence of use increased substantially from 2001 to 2010 and was high among elders. The high number of elderly users, for their general frailty and the potential for interaction with other medications, raises concerns about the impact of severe bleeding adverse events.

228. Anticoagulant Use in Patients with Cancer Associated Venous Thromboembolism: A Retrospective Cohort Study

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Background: Long term anticoagulant therapy with low molecular weight heparins (LMWH) is recommended by clinical practice guidelines for treatment and secondary prevention of venous thromboembolism (VTE) in cancer patients.

Objectives: To assess the LMWH dalteparin, warfarin and other anticoagulant use in adults, cancer patients who also had VTE in Quebec, Canada between 2007 and 2009.

Methods: Data were obtained from the Quebec Health Insurance Agency for 2005–2009. Patients 20 years of age and over were eligible at their first hospitalization for cancer between 2007 and 2009; those with a diagnosis for VTE during that hospitalization or for cancer in the previous 2 years were excluded. Included patients were those discharged alive from the hospital after incurring a VTE (index date). They were followed for 6 months.

Results: Among 953 study patients, 73.2% received anticoagulant therapy at index date; only 61% of them received it for ≥80% of follow-up days (persistent). Anticoagulant use was more likely in heart failure, lower income patients, those discharged from hospital with a primary discharge code of VTE and those concurrently using corticosteroids. Anticoagulant use was less likely in cerebrovascular and blood disease patients and among those who had previously used anticoagulants. Warfarin was less likely than dalteparin in corticosteroid users, and more likely in lower income and cardiac disease patients and in those with a primary discharge code of VTE. No patient characteristic was associated with persistence on treatment.

Conclusions: Many cancer patients did not receive anticoagulant therapy for secondary prevention of VTE as recommended by treatment guidelines; use of anticoagulants is suboptimal in this patient population.

229. The Association between Use of Serotonergic Antidepressants and Perioperative Bleeding during Hip Replacement – A Retrospective Follow-Up Study

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Background: In vitro studies have shown that selective serotonin reuptake inhibitors (SSRIs) inhibit platelet aggregation. It is controversial whether use of SSRIs can cause clinically important bleedings; results from observational studies have been equivocal.

Objectives: Our objective was to determine a possible association between use of serotonergic antidepressants and intraoperative bleeding during hip replacements.

Methods: We conducted a retrospective study among patients that underwent a primary unilateral uncemented total hip arthroplasty (THA) in the Region of Southern Denmark between 1 January 2007 and 28 February 2011. Information was collected on blood loss and the need for transfusions in this group. We compared the blood loss between users of serotonergic antidepressants, users of nonserotonergic antidepressants and non-users. Data on drug exposure were retrieved from the Odense Pharmacoepidemiological Database (OPED). Adjustment for drug-related confounders was carried out by linear regression.

Results: We indentified 638 patients that underwent a THA in the study period. The adjusted difference in blood loss among respectively, users of serotonergic antidepressants and non-serotonergic antidepressants were 62.2 mL (95% CI, -10.1 to 147.5) and 22.9 mL (95% CI, -101.6 to 147.5) compared with non-use.

Conclusions: Use of serotonergic antidepressants was associated with a non-significant increased blood loss compared to non-users.

230. Identification of Hemophilia Patients in Medicaid Claims Data

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Background: The presence of specific diagnostic codes within an administrative data source does not necessarily identify patients with the corresponding medical conditions, and medical records may not be available to inform the degree of correspondence between the code and the condition.

Objectives: To develop an algorithm for identification of hemophilia patients, including those with neutralizing antibodies (inhibitors) to factor VIII or factor IX, in Medicaid claims data in the absence of access to medical records.

Methods: We identified patients who received recombinant factor VIIa (rFVIIa), factor VIII inhibitor bypass activity (FEIBA), factor VIII or factor IX or had a diagnosis code for coagulation defects (ICD-9 286.xx) in the Medicaid Analytic Extract (MAX) database restricted to 44 states and DC for the years 2000–2004. Several algorithms based on combinations of ICD-9 codes, medication use (particularly factor use) and restriction to males were applied to identify patients with hemophilia A and B, as well as patients with inhibitors to factors VIII or IX. Demographic characteristics, additional medical diagnoses and drug use were tabulated in each group to assess the appropriateness of the definitions, by comparing to external information about these disorders based on expected prevalence and clinical manifestations.

Results: From a source population of 63,672,804 enrollees, a total of 130,946 patients had at least one of the codes or medications evaluated, of which 10,693 had a code for hemophilia A (68.2% males) and 2,032 for hemophilia B (76.6% males). Restricting the cohort to males led to subsets of 7,929 patients with hemophilia A and 1,557 with hemophilia B, and these numbers match the expected relative frequencies of these disorders (approximately 4:1). The combination of a single diagnosis, male sex, and receipt of FEIBA or rFVIIa likely identifies patients with inhibitors to factor VIII or factor IX.

Conclusions: Application of external knowledge of target medical conditions can provide a suitable option for improving the accuracy of diagnoses in claims data when medical records are not available.

231. Changes in Platelet Counts over Time in HIV and Hepatitis C Virus (HCV) Co-Infected Patients

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Background: Thrombocytopenia is a clinically significant problem associated with HIV and hepatitis C virus (HCV) co-infection. Low platelet count can increase the risk of bleeding events and interfere with treatment management.

Objectives: To examine platelet count decreases over time among co-infected antiretroviral (ARV)-naïve patients.

Methods: A retrospective study was conducted among ARV naïve patients in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort from 2002 to 2009. Index date was defined as the date of first platelet count during the study period. Patients were censored at the start of ARV or INF therapy, end of study period, or death. Platelet count trajectories over time were modeled using mixed-effects linear regression and adjusted for age, sex, HIV/HCV co-infection, time, baseline CD4 count, and CNICS site.

Results: There were 3,558 HIV mono-infected and 929 HIV/HCV co-infected patients. Co-infected patients were older (42 vs. 37 years of age), less likely to be male (75% vs. 84%), and more likely to report injection drug use as their HIV transmission risk factor (51% vs. 6%). On average, platelet counts decreased by 3.090/μL (95% confidence interval [CI]: -4.100 to -2.080, $p < 0.0001$) per year in ARV-naïve HIV-infected patients. There was an additional decline of 3.630/μL (CI: -5.170 to -2.090, $p < 0.0001$) in co-infected patients when compared to HIV mono-infection.

Conclusions: HIV/HCV co-infection appears to cause a more rapid reduction in platelet counts than HIV infection alone. The number of participants with low platelet count is likely to increase over time. However, low platelet counts are not likely to be a concern for most study participants.

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232. Higher Daily Vitamin K Intake Is Associated with Greater Anticoagulation Stability during Initiation Phase of Warfarin Therapy

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Background: Patients on warfarin are at high risk for bleeding and thrombosis during the initiation phase of therapy due in large part to anticoagulation instability. Although cross-sectional studies have shown that vitamin K rich diets are associated with more stable INRs during maintenance phase of warfarin therapy, it is not known how vitamin K affects INR stability during the critical initiation phase.

Objectives: To determine the independent effects of vitamin K intake on INR stability during the initiation phase of warfarin therapy in a prospective cohort study.

Methods: Baseline data and subsequent INR and dose were derived from a prospective cohort of patients (n = 313) starting warfarin from various US anticoagulation clinics and followed until maintenance phase. Average daily vitamin K intake (ADVK) (μg) was estimated prospectively using a validated patient-recorded 7-day vitamin K diet diary given at enrollment. INR stability was defined as the percent time in therapeutic range (PTTR). Multivariable logistic regressions with ADVK quartiles (ADVKQ1–4) as the exposure and PTTR dichotomized at the median as the outcome were performed. All covariates associated with the outcome with $p < 0.2$ were included in the models.

Results: Median ADVK (mcg) was 82 (36–198) and per ADVKQ was 24 (15–32), 53 (44–69), 125 (98–164), and 293 (239–447) for ADVKQ1–4, respectively. Median PTTR was 79%. In multivariable analysis controlling for identified confounders (standard deviation of daily vitamin K intake over 7-days, history of hypothyroidism, smoking status, marital status, and race), higher levels of ADVK were associated with higher odds of stable INR (PTTR > 79%) compared with ADVKQ1: ADVKQ2 OR = 2.6 (95% CI 1.3–5.3); ADVKQ3 OR = 2.3 (95% CI 1.1–4.8), ADVKQ4 OR = 2.6 (95% CI 0.9–7.4).

Conclusions: Higher ADVK is associated with higher odds of stable INR during initiation phase of warfarin therapy. Nevertheless, the ORs for stable INR did not increase with ADVKQs above the 2nd quartile, suggesting that there may be a threshold effect for ADVK on INR stability. Future prospective studies with more accurate measures of ADVK are warranted.

233. Non-Traumatic Joint Disorders and Analgesic Narcotic Use in Hemophilia A Patients

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Background: Crippling arthritis from repeated hemorrhage into the joints is an adverse outcome in people with hemophilia. The Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends prophylaxis with recombinant factor VIII as the optimal therapy for people with severe hemophilia A or B to prevent joint disease.

Objectives: Determine the prevalence of joint disease and the use of analgesic narcotics in a hemophilia A population enrolled in a US claims database.

Methods: Hemophilia A cases were selected from a US insurance claims database spanning 2004–2010. Cases were defined as having ICD-9 code 286.0 and receiving factor VIII. Two controls matched on age, gender, follow-up time, and benefits were selected for each case resulting in 1,218 hemophilia A cases and 2,436 controls. Frequencies, Odds Ratios (OR), and 95% Confidence Intervals (CI) are presented.

Results: Mean age was 21, with 74% under age 31. Mean follow-up time was 3.5 years. Fifty-eight percent of hemophilia A cases had at least one diagnosis of a non-traumatic joint disorder compared to 25% of controls (OR 4.2, 95% CI 3.6–4.8). Forty-six percent of hemophilia A cases had at least one prescription for an analgesic narcotic compared to 27% of controls (OR 2.4, 95% CI 2.1–2.8); the OR remained consistent across age categories. Among hemophilia A cases with non-traumatic joint disorders, 66% were under age 31. In this age group, the mean number of visits for joint disorders was 5 and 49% had at least one prescription for an analgesic narcotic.

Conclusions: Young hemophilia A patients received diagnoses of non-traumatic joint disorders. The frequency of prescriptions for analgesic narcotics suggests that hemarthroses is causing pain and could lead to crippling joint disease. In a claims database, we are unable to determine if a patient is receiving prophylactic factor VIII therapy. However the high prevalence of non-traumatic joint disorders and the high volume of analgesic narcotic prescriptions suggest that breakthrough bleeding occurs in this young age group of hemophilia A patients despite the recommendation for prophylactic factor VIII therapy.

234. Long-Term Course of the Severe Haemophilia A or B Patients in Sweden: Results from a Cohort Register Study

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Background: The cohort consists of patients enrolled in a large national registry, including 1,431 with haemophilia A or B, born between 1883 and 2008. Registry data were linked to the In- and Out-patient, Cause of Death-, Cancer-, Medical Birth-, Prescription-, Migration- and Multi-Generation registries. Severity of haemophilia was known for 934 out of the 1,431 patients.

Objectives: To evaluate long-term incidence, prevalence and survival in Swedish patients with severe haemophilia.

Methods: The 384 patients with severe haemophilia were compared to 1,918 age and sex matched controls. Kaplan-Meier was used to estimate survival curves. Cox proportional hazard regression models were used to estimate hazard ratio and the follow-up was stopped at 60 years after evaluation of the proportional hazards assumption.

Results: The mean follow-up was 27.1 for the patients with severe haemophilia and for the control cohort 26.1 years. Seventy-eight of the 384 patients were diagnosed with HIV and 167 with viral hepatitis. The hazard ratio for all cause of death was 6.6, 95% CI: (4.1; 10.5), $p < 0.001$. When HIV positive patients were excluded the hazard ratio was estimated to 3.8, 95% CI: (2.0; 7.5), $p < 0.001$. Exclusion of both HIV and/or viral hepatitis gave a hazard ratio of 4.4, 95% CI: (1.6; 12.4), $p = 0.005$. The most frequent cause of death for the patients with severe haemophilia was found to be HIV/AIDS, 22 (28%) followed by haemostatic disorders 16 (20.5%).

Conclusions: This study shows that patients with severe haemophilia have a higher risk of death both with and without HIV and/or viral hepatitis compared to controls. This unique cohort will provide further valuable insight into co-morbidities and allow evaluation of first degree relatives.

235. Evaluation of Second Malignancies in Patients Receiving Bortezomib (Btz)

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Background: Second malignancies (SMs) have been observed at a higher rate in patients with multiple myeloma (MM) than in the general population. Analyses of Btz-treated patients were performed in response to reports of increased SMs associated with maintenance lenalidomide treatment in MM patients.

Objectives: To assess the risk of SM in patients treated with Btz or Btz -containing regimens through evaluation and analysis of three data sources.

Methods: Searches of the Btz global safety database were performed for all medically and non-medically confirmed spontaneous cases, and for all clinical-trial, post-marketing survey, literature, registry, and Health Authority cases involving Btz as a suspect or co-suspect drug in the report of a hematologic or non-hematologic SM through March 2011. Event terms representing malignancies or pre-malignancies were selected through standardized MedDRA queries; review and analysis of cases were conducted using a step-wise algorithm. Data from 4 phase 3, randomized clinical trials of Btz-based therapies in MM were analyzed for the occurrence of SMs; events of neoplasm and new malignancy developing during or after treatment were recorded. Incidence rates (IRs) of SMs per 100 patient-years (py) were calculated. A retrospective observational cohort study of MM patients using the SEER-Medicare linked database (2000–2007) was conducted. IRs per 100 py by Btz exposure status were calculated; multivariate analyses controlled for confounding by prior treatment and other potential risk factors.

Results: For post-marketing cases, 0.0018% and 0.0022% of patients with no clear confounders reported hematologic and non-hematologic malignancies, respectively. In clinical trials, 25 of 1,718 Btz-treated patients developed SMs (5 hematologic, 20 non-hematologic); IRs ranged from 0 to 1.66 in Btz-treated patients. In SEER-Medicare, IRs were 1.83 and 2.29 for Btz and no Btz-exposed patients, respectively, with no difference after adjusting for confounders.

Conclusions: No increased risk of SM among MM patients exposed to Btz was identified. Continued close surveillance and evaluation will be the cornerstone to ensure patient safety.

236. A Comparison of the Effectiveness of Statins in Reducing Total Cholesterol and Low-Density Lipoprotein Cholesterol

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Background: Few previous studies have compared the real-life effectiveness of different statins in reducing lipid values.

Objectives: In this observational study of incident statin use, we compared the effectiveness of different statins in

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reducing total cholesterol and low-density lipoprotein cholesterol (LDL-C)

Methods: We identified all individuals (N = 60,488) from the Helsinki-Uusimaa region of Finland who had started statin use between January 1st, 2007 and December 31st. As the outcome measure, we used lipid measurements that had been taken 1–7 months after the purchase of the first statin prescription. We analyzed the effectiveness of statins in reducing total cholesterol and LDL-C using linear regression, with the difference between the follow-up and baseline values as the dependent variable, and sex, age (categorized into four groups), chronic diseases, baseline values, time since the purchase and different statins as explanatory variables.

Results: The most frequently used statin was simvastatin with 17,515 users. We adjusted for the effects of sex, age, chronic diseases, baseline values and time since the purchase. Compared to simvastatin there was significantly more reduction of total cholesterol levels associated with the usage of atorvastatin (effect 0.11, 95% CI 0.02–0.20) and significantly less reduction associated with pravastatin (0.66, 0.52–0.79), fluvastatin (0.41, 0.31–0.51) and lovastatin (0.35, 0.05–0.65). Usage of the combination of simvastatin and ezetimibe was significantly associated with higher reduction of LDL-C cholesterol, and pravastatin, fluvastatin and lovastatin with less reduction than simvastatin. There was more reduction associated with both rosuvastatin and the combination of simvastatin and ezetimibe, but the association was not significant.

Conclusions: These preliminary results suggest that compared to simvastatin, atorvastatin and seems to be more effective, while pravastatin, fluvastatin and lovastatin may be less effective. However, it should be remembered that because of its low price simvastatin is by far the most widely used statin, and we did not have information on the reasons for choosing another statin than simvastatin as the first statin for the patient.

237. Cancer Risk in Long-Term Users of Vitamin K Antagonists: A Nested Case-Control Study

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Background: Some evidence suggests a protective effect of long-term use of vitamin K antagonists (VKA) against prostate and other cancers.

Objectives: To evaluate if long-term VKA-treatment influences the risk of developing cancer.

Methods:

Design: Matched case-control analysis, using risk set sampling.

Setting: We used data from four Danish nationwide registers. Cases were all Danish individuals with a primary cancer diagnosis (except non-melanoma skin cancer) between January 1st 2000 and December 31st 2009. For each case, we selected eight controls, matched by gender and birth year.

Exposure: A venous thromboembolism may be the first manifestation of a cancer. As VKA are used to treat thromboembolism, this might cause an apparent association. To avoid this bias, we disregarded all prescriptions redeemed < 1 year prior to the index date, i.e., date of cancer diagnosis and corresponding date for matched controls. Long-term VKA use was defined as exposure to VKA for a total period longer than 3 years prior to ≥1 year before index date.

Main outcome measure: Adjusted odds ratios (ORs) for cancer associated with long-term VKA exposure.

Statistical analysis: Potential confounders were controlled by conditional logistic regression. Included confounders were drugs and diseases known or suspected to modify cancer risk and a modified Charlson Comorbidity Index score. Pre-specified sub-analyses were performed for selected cancer sites, sub-groups and measures of exposure.

Results: A total of 238,196 cases were included with 1,713,176 controls. The adjusted OR for cancer associated with VKA use was 1.04 (95% CI, 1.02–1.06) among VKA ever-users and 1.06 (95% CI, 1.02–1.10) among long-term VKA users. Long-term VKA use was associated with increased ORs for alcohol- or obesity-related cancer sites, whereas we observed a decreased risk of prostate cancer (OR, 0.86; 95% CI, 0.77–0.95).

Conclusions: Our large case-control study does not support a general chemopreventive effect of VKA-drugs. However, in accordance with findings from previous studies, we found an inverse association between use of VKA and prostate cancer risk.

238. Renal Function Impairment by Overanticoagulation?

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Background: Recently two cohort studies reported that overanticoagulation defined as International Normalized Ratio (INR) > 3.0 accelerated the decline of renal function. Overanticoagulation is associated with an increased risk of bleeding; however, effects on renal function have only rarely been studied. Because of widespread use of anticoagulation therapy, any such effect would have substantial clinical consequences.

Objectives: To determine whether overanticoagulation (INR > 3.0) was associated with a long-term decrease of renal function.

Methods: We used data from the first cohort of the Rotterdam Study, a prospective population-based cohort study. The study started in 1990 including persons aged 55 years or older. Until 2012, five cross-sectional investigations have been performed while mortality and incident morbidity are continuously monitored. Long-term diabetes mellitus and baseline heart failure were excluded. The outcome of interest was defined as the difference in glomerular filtration rate per year between first, and third or fifth study visit, whichever came latest. Exposure was defined as the cumulative number of episodes of overanticoagulation between the two measurements. We used linear regression to study the association.

Results: In 2,796 participants (61% female, mean age 66 years) overall decline in renal function was 0.44 mL/min/1.73 m^2/year. Male gender, higher systolic blood pressure and the use of anticoagulation therapy in structural heart disease or heart rhythm disorders were associated with an increased decline of renal function. No association with overanticoagulation was observed -0.001 mL/min/1.73 m^2/year ($p = 0.74$), corrected for age, sex, blood pressure, diabetes mellitus, heart failure and duration of – and indication for anticoagulation therapy.

Conclusions: We did not demonstrate an association between overanticoagulation and long-term decrease of renal function.

239. Safety of Off-Label Erythropoiesis Stimulating Agents (ESAs) in Critically Ill Patients: A Systematic Review and Meta-Analysis

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Background: Erythropoiesis stimulating agents (ESAs) are prescribed in critically ill patients to treat anaemia. This indication is off-label, because it is not licensed by regulatory authorities. Recently ESAs were suspected to harm in case of critical illness.

Objectives: To assess the safety of ESAs in critically ill patients.

Methods: On 15 November 2011 we conducted a systematic search on EMBASE, MEDLINE, all EBM reviews, IPA, PASCAL and PsycINFO via OvidSP as well as SCIE, Conference Proceedings Citation Index-Science, CINAHL, BIOSIS Previews and TOXLINE. We considered randomized controlled trials (RCT) and observational studies in any language that compared scheduled systemic administration of ESAs with other anti-anaemia interventions or placebo in critically ill patients. Adverse events and mortality were the outcomes. Two authors independently screened and evaluated retrieved records eligibility, extracted data and assessed risk of bias (ROB) of the included studies. Differences in opinion were settled by consensus or involving a third author. Studies with low to moderate ROB were pooled using random effects meta-analysis.

Results: We screened 8,727 citations and included 26 studies (14 RCTs and 12 observational studies). In overall, 62 adverse events were identified in 16 studies; 56 adverse events were reported in 9 RCTs of 3,442 participants and 14 adverse events were reported in 6 observational studies of 924,180 participants. There were no significant associations between ESAs use and risk of any adverse event (RR = 1.02, 95% CI: 0.96–1.08), deep venous thromboembolism (RR = 1.27, 95% CI: 0.93–1.73), pulmonary embolism (RR = 1.53, 95% CI: 0.79–2.96), renal failure (RR = 1.19, 95% CI: 0.73–1.93), sepsis (RR = 0.97, 95% CI: 0.73–1.29) and pneumonia (RR = 1.27, 95% CI: 0.72–2.24). Meta-analysis of five RCTs and five observational studies showed no increased risk of mortality in critical ill patients receiving ESAs (RR = 0.91 95% CI: 0.65–1.29).

Conclusions: Our findings indicate that ESAs treatment in critically ill patients was not associated with significant increase in most frequently reported adverse events but had no effect on mortality.

240. A Review of Postmarketing Adverse Event Reports from AERS for Dabigatran (Pradaxa)

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Background: In December 2011, the FDA published a drug safety communication on the possible association between dabigatran (Pradaxa) and serious bleeding events. Dabigatran was approved in the United States in October, 2010.

FDA AERS data is available at little or no cost. This data has been used in the past, but is often criticized. Used carefully, it is one of the best sources of safety signals.

Objectives: To review AERS reports of Dabigatran from October, 2010 through September, 2011 to determine the existence of signals singly and in comparison to warfarin and all drugs.

Methods: FDA AERS data was extracted for any report containing Pradaxa* or dabigatran*. The last best case of each report was computed as well as the seriousness and suspect status. For each reaction, we calculated the date the term first appeared on a report for the proper time trend analysis. Percentages of adverse events were calculated at various points in time. Data for warfarin as well as the overall background of all drugs were compared to Pradaxa. Although not in possession of the company

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database, reports from the manufacturer were extracted to estimate what was in the possession of the company at various points in time.

Results: There were approximately 10,000 unique reports in the database including approximately 4,300 reports with the drug considered suspect and serious. There were some 1,200 reports of the MedDRA HLGT "gastrointestinal haemorrhages NEC."

A comparison of percentages of serious, suspect reports shows that even as early as 12/31/2010, there was a substantial signal of GI haemorrhages as compared to warfarin or the background of all drugs.

Conclusions: A review of the dabigatran data shows that routine pharmacovigilance shows various signals of concern with this new drug. Because the FDA AERS data is publicly available for little or no cost, this tool should be used as a valuable component of pharmacovigilance.

241. Abstract withdrawn by author.

242. The Role of Spontaneous Events Databases for Benefit-Risk Analysis

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Background: Benefit-Risk analysis of drugs is being increasingly requested for rational decision-making. Safety assessment is traditionally based on meta-analysis where the number of adverse events (AE) in controlled placebo/untreated and head-to-head studies is limited.

Objectives: We used the World Health Organisation database (Vigibase) to evaluate the contribution of a global spontaneous AE database for an analysis of benefit-risk for Glatiramer acetate (GA) in multiple sclerosis.

Methods: Vigibase is a passive surveillance system that in 2011 contained over 6 million reports of spontaneous AEs suspected of being linked to health care products from regulatory authorities in nearly 90 countries. GA, interferon beta-1a, interferon beta-1b (interferons) and natalizumab and the reactions suspected of being associated with them were identified. Disproportionality analyses used the Multi-item Poisson Gamma Shrinker method with WHO-ART diagnosis at the preferred term level for all AEs and for the standard combination of all WHO "critical terms." Statistical significance for disproportionality was defined as an Empirical Bayesian Geometric Mean lower fifth percentile (EBGM05) >2.0. Comparisons were made between GA vs. all other drugs and GA vs. interferons and natalizumab. Sales data for GA were available to calculate reporting rates.

Results: A total of 2,320 cases with 6,680 AEs with a suspected relationship with GA and 20,155 cases with 72,326 AEs for interferons and natalizumab were identified. Compared with all other drugs in Vigibase and with interferons and natalizumab, GA was associated with several statistically significant observations of disproportionate reporting. WHO "critical terms" combined were not higher for GA vs. interferons and natalizumab (EBGM of 0.84 (90% credibility interval 0.79–0.90). The reporting rate of WHO "critical terms" for GA was 69 events/100,000 person-year.

Conclusions: When safety data from clinical trials are scarce, the analysis of a global large spontaneous AEs database permit the assessment of non-common and important risks. However, the biases inherent in these databases need to be addressed.

243. Case-Crossover Studies in the Presence of Exposure Time Trends and Immeasurable Time

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Background: Self-controlled designs such as the case-crossover and the self-controlled case series designs use within-person comparisons to control for time-invariant confounders, but do not control for time-varying confounders such as changes in exposure probability over time. The case-case time-control design uses between-person comparison of trends to add an adjustment for exposure-time trends to the case-crossover estimate.

Objectives: To demonstrate the potential impact of exposure-time trends in a self-controlled design setting by conducting example studies using three claims databases covering different populations and with different information content.

Methods: We investigated the association of intermittent antipsychotic medication prior to hospitalizations for ischemic stroke or myocardial infarction (MI) using administrative claims data from the Veteran's Health Administration (VA), British Columbia (BC), and the Pharmaceutical Assistance Contract for the Elderly (PACE). The VA has in and outpatient dispensing data from its facilities linked at the patient level, however BC and PACE do not have linked inpatient medication dispensing, thus medication exposures during time spent in hospitals are immeasurable.

Results: Our results illustrate the point that the impact of exposure-time trends on effect estimates when using a self-controlled design can be non-trivial. The non-causal trend in exposure over time estimated in the three data sources for the two outcomes ranged from null to a threefold increased probability of exposure during the "case" time

window relative to exposure probability in the "control" time window.

Conclusions: Using cases as their own time-controls to adjust for exposure-time trends can help reduce the impact of bias due to reverse causality and bias due to immeasurable time.

244. Use of Multiple Sources and Capture-Recapture Method to Estimate the Frequency of Hospitalizations Related to Drug Abuse

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Background: It is necessary to quantify serious hazards of psychoactive drug abuse or misuse to better understand the harm caused. One of the major difficulties of assessing these disorders is that addictive behaviours are often associated with hidden characteristics that are difficult to detect by usual approaches.

Objectives: This study aimed to estimate the incidence of serious drug-related complications by using the capture-recapture method in defined geographical area.

Methods: The study was conducted in the university hospital of Toulouse, France. Hospitalizations with mention of disorders related to drug of abuse were considered serious drug-related complications. We searched these cases in and crossed three sources of data: spontaneous reports of drug of abuse related disorders (NotS) collected by the regional addictovigilance centre, computerised hospital database PMSI (Programme de medicalisation des systemes d'information), and toxicological analyses (TA) carried out for hospitalized patients. Log-linear regression modelling was used for capture-recapture analysis.

Results: In 2007 and 2008, 1,509 distinct cases were captured. After data modelling, the estimated number of psychoactive drug-related hospitalizations was 4,744 (95% confidence interval: 4,060–5,429). Most frequent products were opioids (34%), cannabis (19%) and cocaine (13%). "Multiple drugs" were observed in 26% of cases. Incidence of serious drug-related complications in the area covered should be estimated at 5.7 (5.5–5.9) per thousand 15–64 year old inhabitants. Exhaustiveness of sources were 0.4% (0.2–0.6) for NotS, 11.6% (10.7–12.5) for TA and 22.6% (21.4–23.8) for PMSI.

Conclusions: The "real" number of cases far exceeds that of cases which can be identified through simple counts. In particular, it confirms the under-reporting and even quantifies its magnitude. These results confirm that drug users are frequently hospitalized and require heavy medical management. Moreover, these results show the real although limited advantage of hospitalization database in detecting drug associated disorders in epidemiological studies.

245. Health Screening Participation and Risk of All-Cause Mortality

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Background: In Japan, employees are mandated to undergo free annual health screenings. Some health insurance unions additionally offer similar optional screening programs to their family members, though the participation rates are far from 100%. Employees and their families who do not participate may be different from those who participate in their life style and health seeking behaviors.

Objectives: To assess the association between health screening participation and all-cause mortality.

Methods: We obtained healthcare utilization data for 491,292 beneficiaries covered by four large private health insurance unions from Japan Medical Data Center. We restricted the study population to 315,184 beneficiaries aged between 20 and 74 years between April 1, 2005 and March 31, 2011 and remained enrolled for the first 365 days. Subjects were considered exposed if he or she did not participate a health screening during the first 365 day period. If non-participants participated in a screening during the follow-up period, they were considered censored. We identified deaths using enrollment and/or claims data. We assessed the association between participation to screening and mortality using Cox proportional hazard regression adjusting for age, sex, use of health care services, comorbidities/use of drugs for major comorbidities.

Results: For 243,720 employees with 63% of males and mean age of 34, we observed 275 deaths during 435,818 person-years of follow-up. Among 71,464 family members with 8% of males and mean age of 38 years, 199 died during 126,609 person-years. Mortality ratio adjusted by age and sex was 1.4 (95% CI: 1.0–1.8) for employees but more pronounced in their family members with the ratio of 2.5 (95% CI: 1.7–3.8). After adjusting for measured confounders, the hazard ratio was 1.1 (95% CI: 0.9–1.5) for employees and 2.2 (95% CI: 1.4–3.3) for their family members.

Conclusions: Non-participation to a health screening was associated with twofolds increased risk of death for family members. Our study suggests that health screening participation by choice may be a surrogate for health seeking

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behaviors and potentially used to control for healthy user bias in pharmacoepidemiology studies.

246. Up in Smoke! Capturing Smoking History from Clinical Notes

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Background: Tobacco use affects many diseases and treatments, including rheumatoid arthritis. Smoking status and quantity is usually recorded in text notes and a tool is needed to extract and structure the information for epidemiologic studies.

Objectives: While smoking information is clinically important, it is difficult to use in retrospective analyses without chart review. As part of the VA Rheumatoid Arthritis Registry, we developed an algorithm to detect smoking status and capture pack-year information.

Methods: Our approach was to classify each mention of smoking information in preparation for a patient level determination. This allows flexibility when dealing with changing status over time. Machine learning was used to classify the instance as "current smoker," "past smoker," "non-smoker," or "unknown." Each patient may have many instances, and for this study we used the most common instance classification as the patient's status at their most recent visit. Text surrounding terms like "smok*," "cigar," and "tobacco" was then processed using patterns for numeric values of quantity, frequency, and duration. These were extracted individually and multiplied to yield pack-years.

Results: Of 225 patients were manually reviewed, of which the smoking status was predicted correctly 182 times (80.8%), with a total of 11,142 instances. Prediction of current smokers was correct 48/50 (96.0%), non-smokers was correct 52/55 (94.5%), and whether a patient has ever smoked or not was correct 211/225 (98.6%). Former smokers were the most difficult to classify, with 82/120 correct (68.3%). Of the 38 misclassified former smokers, 27 (71.0%) were classified as current and 11 (29.0%) were classified as non-smokers.

Conclusions: This method is effective at classifying current smokers, non-smokers, and lifetime use of tobacco, thus facilitating large-scale use of smoking information for research and quality measures on current smoking behavior or risks associated with use. The most difficult classification is former smokers because the notes often indicate non-smoker without indicating the patient formerly smoked.

247. Development of a Web-Based Interactive Tool to Display Cohort Characteristics from a Variety of Patient Populations and Data Sources

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Background: Basic descriptive statistics are commonly generated for patient cohorts used in any pharmacoepidemiologic study, often in a single large excel file with many worksheets. For an epidemiology department, it is difficult to quickly review all the the cohorts previously created across disease areas and compare characteristics for a given cohort across data sources.

Objectives: To develop a web-based interactive tool to easily identify patient cohorts and display descriptive cohort characteristics.

Methods: As claims and electronic medical record data sets are commonly available as SAS files, we used SAS to define criteria which were used to create cohorts. Cohort-specific results were output in defined templates that contained all the descriptive characteristics of the cohort, which can include breakdowns by demographics, comorbidities, medications, lab values, etc. These output files were easily uploaded and automatically parsed into a database structure through a drag-and-drop mechanism. The tool was developed to be flexible enough to receive any type of descriptive information about the cohorts. The web tool displays cohorts by therapeutic area and disease area. Users can search for or browse the available cohorts. Since cohorts can be defined differently in each disease area, a basic attrition table is displayed which shows the number of patients and the criteria used to define each of the cohorts. When the user selects a cohort, the website displays all the available descriptive cohort characteristics. The user can toggle between reports and choose to view the results in a tabulated or graphical format. The user is also given the option to download all the results in an excel file (tabulated) or pdf file (graphical format). Information for cohorts defined with the same criteria can be compared across data sources.

Results: This system was developed and tested using analysis results from 45 cohorts covering 15 medical conditions.

Conclusions: This tool provides an easy way to upload analysis results and quickly explore them across different medical conditions and data sources.

248. Analysis of Unbalanced Contingency Tables of Web-Based Potential Adverse Event Reports

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Background: Alternative to spontaneous reporting systems are being developed. These new data sources present different statistical challenges.

Objectives: The objective of this paper is to examine different methods of analyzing large unbalanced contingency tables generated from patient web forums using natural language processing. The generated contingency tables are unbalanced compared to spontaneous reporting systems because the NLP has to be set to search initially for specific drugs and for specific conditions based on the initial training set.

Methods: Using a dataset of 1,000 products and 2,284 conditions we tested the sensitivity of standard disproportionality methods to influential cells, rows, and columns. We computed the point estimate and 95% confidence interval for the proportional reporting ratio (PRR), reporting odds ratio (OR), and the Bayesian Confidence Propagation Neural Network (BCPNN) implementation of the information component. Four methods of removing balance and noise problems were tested: requiring cells counts of at least 10, requiring at least 100 reports from an individual drug or for an event, removing Pearson residuals above 2.0, and removing rows and columns with more than 5,000 observations in the dataset.

Results: The data consisted of 2,284,000 cells, of which 96.81% had no observations. The baseline estimates without restriction found 27,195 statistically significant ($p < 0.05$) drug-event combinations using the PRR, 27,052 using the ROR, and 9,014 using the BCPNN. Requiring counts of at least 10 reduced statistically significant effects to 5,261, 5,332, and 5,373. The Pearson residual criterion reduced significant cells to 9,448, 9,282, and 4,394. Using cerivastatin and rofecoxib as test cases, muscle weakness manifesting as back pain was identified by BCPNN in all methods except for when 100 reports or 10 events per cell were used for deletion. No significant cardiovascular effects were found for rofecoxib.

Conclusions: No method completely removes noise without also eliminating known signals. Using preliminary data, limits of 10 events per cell may be too restrictive in small contingency tables.

249. Prevalence of Comorbidity of Chronic Diseases: A South African Pharmacy Benefit Management Company (PBM) Database Analysis

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Background: The major impact of chronic diseases, with regard to their large disease burden and associated costs, has placed them at the fore of international and South African (SA) strategic health priorities. Integral to this is the increasing number of patients with multimorbidity of chronic conditions.

Objectives: To determine the prevalence of comorbidity of the most prevalent chronic diseases (as defined in the SA Chronic Disease List [CDL]).

Methods: A cross-sectional study was conducted. Data were obtained from a SA PBM company for 2008. The database consisted of 974,497 patients. The CDL included all chronic disease ($n = 26$) that must be covered by medical schemes as part of the prescribed minimum benefit package.

Results: A total of 190,519 patients (19.5%, $n = 974,497$) had ≥1 CDL conditions, with an average number of 1.60 (SEM = 0.001; 95% CI, 1.598–1.601) CDL conditions per patient. 56.0% ($n = 106,698$) of these patients had only one CDL condition, 28. 8% ($n = 54,782$) had two, 11.28% ($n = 21,486$) had three and 4% ($n = 7,553$) had more than three. The most prevalent CDL conditions were hypertension (64.3%), hyperlipidemia (32.6%), Type 2 diabetes (15.8%), hypothyroidism (14.9%) and asthma (4.4%). Hypertension patients experienced an average of 1.83 (SEM = 0.003; 95% CI, 1.82–1.84) CDL conditions: only hypertension (44.4%), hypertension with hyperlipidemia (15.1%), hypertension and Type 2 diabetes (6.9%), and hypertension with hypothyroidism (5.0%). Patients with hyperlipidemia had an average of 2.24 (SEM = 0.003; 95% CI, 2.23–2.25) CDL conditions: hyperlipidemia with hypertension (29.4%), only hyperlipidemia (23.1%), hyperlipidemia with hypertension and Type 2 diabetes (8.3%). Type 2 diabetes patients had an average of 2.40 (SEM = 0.005; 95% CI, 2.39–2.41) CDL conditions: Type 2 diabetes with hypertension (27.9%), only Type 2 diabetes (19.3%), Type 2 diabetes with hypertension and hyperlipidemia (17.2%).

Conclusions: This study emphasised the need for increased research to provide an appropriate scientific basis on which to build evidence based care guidelines for patients with multimorbidity of chronic conditions.

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250. Using Natural Language Processing of Electronic Health Records to Identify Patients with ANCA-Associated Vasculitides in the Veterans Affairs

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Background: Studying patients with an ANCA-associated vasculitis (AAV) is a challenge due to difficulty in distinct case ascertainment between subtypes using only ICD-9 diagnosis codes: Granulomatosis with polyangiitis (Wegener's, GPA), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS). One code is designated for GPA (ICD-9,446.4); however, this code is often used for the other AAV subtypes. Having only one specific code to identify these diseases makes it difficult to distinguish between the subtypes and underestimates the number of MPA and CSS cases. In addition, AAV is rare, requiring a large population for meaningful research. Electronic Health Record (EHR) data provide more granular information via the narrative text of clinical notes.

Objectives: Our objective was to use Natural Language Processing (NLP) to accurately identify patients with an AAV in a large, population-based database.

Methods: The Department of Veterans Affairs (VA) is the largest health care system in the U.S., providing care for approximately 6 million active veterans at over 1,400 points of care. The VA EHR database contains over 20 million patients. Using this database, we applied NLP to extract text from clinical notes that could identify the type of AAV the patient was diagnosed with. Clinical specialists and NLP experts determined various ways physicians document an AAV diagnosis in their clinical notes. These terms were used to develop and train the NLP, which was then validated against manual chart review to determine it's accuracy and reliability in identifying these AAV cases.

Results: Of 2,204 patients were found with ICD-9 code 446.4 in the VA between 1/1/1999 and 12/31/2011. Further results, including detailed NLP validation and exact counts of patients for each subtype of AAV, will be presented.

Conclusions: This study utilized NLP to leverage identify patients with medical conditions that are more granular than available diagnosis codes. In a follow-up study, AAV cases will be compared to commonly used AAV-related ICD-9 codes. In addition, AAV cases will be furthered studied in terms of clinical characteristics and specific outcomes of interest.

251. Impact of Pharmacy Benefit Eligibility on Morbidity in a US Medical Claims Database

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Background: US medical claims databases are often used to calculate background rates when evaluating adverse events. Not all beneficiaries have concurrent pharmacy benefits; however, it is often unclear whether these beneficiaries truly are without pharmacy benefits or have benefits not captured in the database. Potential biases introduced by the inclusion/exclusion of these beneficiaries have not been well studied.

Objectives: This study's objective was to estimate the impact of pharmacy benefit eligibility on the prevalence and incidence of morbidity and health care utilization in a large US medical claims database.

Methods: A random sample of medical beneficiaries in a large US medical claims database with continuous enrollment from 2004 to 2007 was selected for this cohort study. Only beneficiaries with either concurrent or no record of pharmacy benefits during this period were included. Morbidities were summarized by a score developed by Gagne et al. Healthcare utilization was summarized by the number of outpatient and emergency room encounters and total days hospitalized each year. Longitudinal trends in morbidity and health care utilization were assessed using generalized estimating equations.

Results: At baseline, beneficiaries without pharmacy benefits (n = 1,515,455) had greater morbidity summary scores than beneficiaries with pharmacy benefits (n = 1,513,682) (0.037 vs. 0.031, $p < 0.0001$) and had more outpatient encounters, but fewer emergency room encounters and shorter hospitalizations. Of the 20 morbidity categories in the summary score, patients without pharmacy benefits had an increased risk of 5 morbidities but a decreased risk of 13 morbidities (Odds ratio: 0.87–1.23). The between group difference in rate of change in the comorbidity score was characterized by β (no pharmacy benefits) = -0.008 and β (no pharmacy benefits × year) = 0.008.

Conclusions: Beneficiaries without pharmacy benefits had a small but statistically significant increase in baseline morbidity, but overall had a lower risk for incident morbidity and had a differential pattern of healthcare utilization. Further study should evaluate the impact of these differences on medical claims studies.

252. Self-Controlled Design in Pharmacoepidemiology: Systematic Review of Methodology and Application

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Background: The use of self-controlled designs in pharmacoepidemiology has undergone considerable growth. Commonly used designs include case-crossover (CCO) design in which each case serves at its own control during different periods, and self-controlled case series (SCCS) designs in which each case's given observation time is divided into control and risk periods.

Objectives: To systematically review for CCO and SCCS used to study the relationship between drug use and outcomes including morbidity, mortality, compliance, from the standpoint of methodology and application.

Methods: A search was made of the MEDLINE and EMBASE databases, with keywords of "case crossover," "case-crossover*," "self controlled case series," and "self controlled design*." Among the searched studies, we excluded studies not related to pharmacotherapy (Non-I), and review or comments papers (Non-S). As methodological view, the following information was extracted: author; study location; year; data source; type and number of population; type of self-controlled design; exposure variable(s); outcome variable(s); number and length of risk windows (case/ control periods) and risk intervals, controlling confounding factors; and whether or not effect modification was analyzed.

Results: The review covered 102 papers that fulfilled the inclusion criteria. Of these, 62 were CCO, and 40 were SCCS. The most frequent outcome variables were those relating to hospitalization. Eighteen percent of studies were registry-based, and 72% of studies used claims database. Among SCCS studies, 25 (62.5%) were related to vaccine safety. Length of risk windows ranged from hours to 180 days. As the statistical analysis, 92% of CCO studies and 90% of SCCS studies controlled for potential confounders or effect modifications.

Conclusions: Variable types of exposure/ outcome windows and statistical methods have been applied. The results can provide guidelines for the design, analysis, and reporting of studies that employing self-controlled designs in pharmacoepidemiology.

253. Using Marginal Structural Logistic Modelling for Risk Ratio Estimation in Longitudinal Pharmacoepidemiological Studies

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Background: Logistic regression is one of the most commonly used statistical models used in pharmacoepidemiological research. While the odds ratio (OR) estimated in such models provides a close approximation of the risk ratio (RR) when the outcome is rare, other approaches are needed when the outcome is relatively common. Zhang and Yu (JAMA, 1998) proposed a method that has gained considerable popularity but was subsequently shown to produce biased estimates. We hypothesize the use of marginal structural logistic modeling (MSLM) can enable valid translation of logistic-regression-based estimates of the OR to the RR.

Objectives: To assess the performance of MSLM in RR estimation in longitudinal pharmacoepidemiological studies.

Methods: We carried out a series of statistical simulations comparing the performance of several methods of estimating the RR: (1) "naive" OR approximation to the RR; (2) the Zhang and Yu method; (3) MSLM; (4) log-binomial regression modeling; (5) Poisson regression modeling; (6) Cox proportional-hazards modeling. Several scenarios were considered: (1) OR is constant across the covariate strata and the covariate is not a confounder; (2) RR is constant across the covariate strata and the covariate is not a confounder; (3) OR is constant across the covariate strata and the covariate is a confounder; (4) RR is constant across the covariate strata and the covariate is a confounder.

Results: In the context of inconstant OR but constant RR across covariate strata, the Zhang and Yu method is biased when used for estimation of both the effect on the average risk in the whole population and the effect in the individuals at the average risk. Moreover, this bias prevails even in the absence of confounding. In the context of both constant and non-constant ORs across strata, the MSLM-based method allows unbiased estimation of the RR. The MSLM-based method is asymptotically unbiased both in presence and absence of confounding.

Conclusions: Marginal structural logistic regression modeling provides an unbiased and reasonably precise method of RR estimation in longitudinal pharmacoepidemiological studies.

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254. Implications of Immortal Time When Outcomes Are Non-Fatal

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Background: Misclassification or exclusion of immortal time can bias effect estimates toward showing a protective effect of exposure, often severely. However, the amount of bias introduced in studies with non-fatal outcomes is unclear.

Objectives: To develop a framework to quantify the magnitude of bias from mishandling immortal person-time in studies with non-fatal outcomes within the context of an applied example.

Methods: We extended Suissa's formula for quantifying bias from excluded immortal time to settings with non-fatal outcomes, assuming a constant rate of outcome. We then quantified event-depleted (immortal) time bias within a cohort study with a largely non-fatal outcome. In this study, patients were preferentially accrued into the exposed cohort even where prior eligible exposure to a comparator existed. We then reconstructed these cohorts with persons entering the cohort for which they first qualified, thereby avoiding the exclusion of event-depleted time by assigning it (and events occurring during it) to the correct cohort.

Results: In the study, 37% of patients in the exposed cohort had eligible comparison exposure prior to cohort entry. However, the incidence rates were similar in both formulations of the cohorts, suggesting that there was little or no bias from the excluded event-depleted time. Assuming that the excluded event-depleted person-time for the 37% of patients was 66% as long as the person-time in the comparison cohort and that the incidence rate in the comparison cohort was twice that in the event-depleted time, there would be an appreciable underestimation of rate ratios (% bias = 80%). Had the event-depleted time been completely event-free, the percent bias would have been 60%. Graphical depictions of the percent bias provide a visual demonstration of the effect.

Conclusions: The magnitude of event-depleted time bias depends on the ratio of incidence rates in the event-depleted time and the comparison cohort, and the amount of excluded or misclassified person-time. In plausible scenarios, the resulting bias can be negligible or appreciable depending on these parameters, and can be quantified in a straightforward fashion.

255. Methods to Improve Study Representativeness in Prospective Observational Research

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Background: Prospective observational studies enable the evaluation of efficacy and safety of medications in a more diverse population as compared to randomized clinical trials. Furthermore, the objective of such a study design may be to understand how a medication is utilized in a real world setting.

Objectives: The objective of the current study is to describe analytical methods that can be implemented to improve study representativeness with respect to a target population.

Methods: The development of an enrollment model will be described. The enrollment model includes sections describing site identification, site selection, and patient enrollment. The purpose of developing an enrollment model is to understand the distribution of key population parameters and how best to select patients and sites.

Results: Once the disease and geographical target populations are determined, one can utilize disease incidence/prevalence data to model the patient distribution for the study population. For instance, the GLOBOCAN database provides country-specific prevalence and incidence estimates for numerous cancer types. Within each country, a feasibility assessment can be used to identify sites that treat the disease of interest and determine the distribution of other site parameters (e.g., urban vs. rural; various physician specialties). Site selection for a study is based upon the site identification findings. The number of sites selected per country should be proportionate to the overall disease population estimates. For example, if 10% of the target disease population is located in France, then 10% of the sites should be allocated to France. Furthermore, sites may be selected within a country aligned with the distribution of a country-specific site parameter. Lastly, patient enrollment should be based on a systematic approach (i.e., consecutive enrollment) to reduce physician selection bias. Site enrollment caps may be utilized to reduce the likelihood of over enrollment in a given location or site type.

Conclusions: When designing a prospective observational study, population estimates can be utilized to improve the representativeness of the study population with respect to the target population.

256. A Framework for Simulation Studies Based on Complex Healthcare Utilization Data for Methods Evaluation

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Background: Monte Carlo simulation is a popular tool for studying the performance of statistical methods. However, the performance of new, computationally intensive methods for confounding adjustment rests on the information available in healthcare claims databases. The data-generating models used for simulation studies evaluating these methods should reflect the complex relationships among the thousands of measured variables in these databases.

Objectives: To develop a framework for simulating data that have a known exposure effect while preserving the complex covariance structure among covariates and exposure observed in an empirical claims database.

Methods: In this framework, exposure, follow-up time and covariates are drawn from observed claims. The estimated multivariate association between covariates and outcome is used with a specified event rate and exposure hazard ratio (HR) to calculate the probability of outcome for each patient, based on his covariates and follow-up time. Binary outcome variables are simulated with these probabilities. To evaluate our framework, we applied it to a sample of 100,000 patients in a national insurance claims database who initiated simvastatin plus ezetimibe or a statin alone. We extracted 61 pre-exposure covariates and followed patients for a composite cardiovascular outcome. We simulated 500 outcome variables with a HR of 1.0 and an event rate of 4/100 person-years.

Results: In the simulated data, the mean event rate was 3.9 (SD: 0.1), close to the target value. The covariance among covariates and exposure was identical in observed and simulated data. Associations between covariates and outcome were also similar in observed and simulated data; for example, the crude rate ratio between prior myocardial infarction and outcome was 3.5 in observed data and 3.4 (SD: 0.3) on average in simulated data.

Conclusions: The Monte Carlo simulation framework created datasets that reflected the observed complex data structure, but had the advantage of an investigator-specified event rate and exposure effect. This framework can be used to evaluate methods for comparative safety and effectiveness analyses in realistic data.

257. A Hybrid Empirical/Simulation Approach to Testing the Performance of the High-Dimensional Propensity Score

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Background: The automated high-dimensional propensity score (hd-PS) algorithm, which empirically selects variables for propensity score (PS) inclusion based on frequency, prevalence and potential to cause bias, has been shown to perform as well as or better than investigator-driven covariate selection in a variety of datasets, but has not been tested in simulation. Since the algorithm relies on the complex inter-variable relationships in real-world datasets, fully synthetic simulation settings is not sufficient.

Objectives: We created a simulation environment that maintained the complexity of real-world data but added a known treatment effect, and employed it to test the performance of the hd-PS algorithm against standard multivariate adjustment.

Methods: From administrative claims data, we sampled 100,000 patients out of a cohort of 344,857 individuals 65+ who initiated either statin therapy alone or simvastatin plus ezetimibe. We followed these patients for a composite cardiovascular outcome. We also collected data on 61 confounders. For each patient, we calculated a probabilty of outcome based on observed multivariate confounder-outcome associations and an investigator-specified hazard ratio (HR) of 1.0. We simulated 100 outcomes per patient; to allow for a rich propensity score (PS), exposure distribution and confounder-exposure associations were unmodified. We applied multivariate adjustment and compared the results to adjustment by a PS including age, sex, and 500 variables selected by hd-PS from among all drug dispensings and inpatient and outpatient diagnoses and procedures, recorded in the 6 months prior to treatment initiation.

Results: Across the 100 simulations, the mean crude HR was 0.92; age/sex adjustment raised this HR to 0.95. Multivariate adjustment yielded a mean HR of 0.97. Replacing multivariate adjustment with adjustment by hd-PS also yielded an HR of 0.97. Standard errors were similar.

Conclusions: In our study, hd-PS provided confounding adjustment that was as good as investigator-driven variable selection. The hd-PS approach can offer bias reduction with minimal investigator input, and may be suitable for use in automated systems.

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258. Propensity Score Development in a Rare Disease Registry

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Background: Rare diseases have very small patient populations and have variable severity/progression, age at diagnosis, and regional treatment patterns that make analysis of outcomes difficult. Registries have been established to track the disease and treatment outcomes of some rare diseases. Varying patient characteristics and ethical implications of withholding treatment in a clinical trial control group make it difficult to study effects of prompt initiation of treatment after diagnosis.

Objectives: Assess the feasibility of creating a propensity score (PS) for registry analyses comparing prompt initiation of treatment after diagnosis with delayed treatment initiation in adult patients in a rare disease registry.

Methods: We identified adult treated patients in the registry with symptom onset >12 months of age who initiated treatment after commercial availability and were not invasively ventilated at treatment initiation. We evaluated the distribution of demographic/clinical characteristics across time to treatment initiation period (early vs. delayed treatment, defined by the median time to treatment initiation) and outcome (invasive ventilation or death). Inclusion of variables in the PS was based on a p-value ≤0.10 in the relationship with both the exposure and outcome. Odds ratios (ORs) and 95% confidence intervals (CIs) from the PS model are reported.

Results: The registry contained 1,003 patients (October 2011); 404 treated adult patients met study entry criteria. Median time to treatment was 12.1 years; 25 patients had a record of invasive ventilation or death. In the PS model, ORs for receiving earlier treatment initiation were 0.96 (95% CI 0.95, 0.98) for age at treatment initiation ($p < 0.001$), 0.48 (95% CI 0.30, 0.74) for having a respiratory symptom ($p = 0.001$), and 1.90 (95% CI 1.22, 2.94) for receiving a diagnosis in 2009–2011 compared with 2006–2008 ($p = 0.004$). The PS model had a c-statistic of 0.69.

Conclusions: There are important confounders in the relationship between early treatment initiation and invasive ventilation or death that must be addressed. A small patient population limits use of multiple covariate adjustments. Implementing the PS methodology is feasible in a rare disease registry.

259. Bootstrap-Based Aggregation Method for Distributed Time-to-Event Analyses of Medication Effects

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Background: Pharmacoepidemiological studies of drug effects on clinical outcomes performed across several countries (or jurisdictions), with the constraint that individual-level data cannot be shared between the countries, require using aggregation methods for combining results obtained from each country. However, in complex models where, for example, the drug-outcome relationship is represented by a function, standard meta-analysis methods cannot be used.

Objectives: Develop and validate an aggregation method for distributed analyses done with standard or complex time-to-event models, without having to pool data from the different sites or transfer individual-level data from one site to another. Develop an adequate procedure for testing the statistical significance of the drug effect and heterogeneity of effects across sites.

Methods: We propose a new computationally intensive aggregation method requiring that each site fits the model to its data and applies a non-parametric bootstrap. Resulting regression estimates are transferred to a data analysis center that aggregates estimates and uses a double-bootstrap for estimating confidence intervals (CIs). We validated the method in simulation studies with different scenarios assuming that treatment effects are homogeneous or heterogeneous across sites. The Cox model was used for the analyses. Results from the proposed method were compared to the ideal (gold standard), but practically unfeasible, method of pooling individual-level data from the different sites and fitting a Cox model on this pooled dataset.

Results: Unbiased estimates of the drug effect were obtained for the proposed method and estimates were highly correlated ($r \geq 0.99$) with those from the pooled data analysis. CIs were 30% to 220% wider for the proposed method, with wider CIs when the heterogeneity of drug effects was larger across sites. Power and type I error rates obtained from the proposed testing procedure were similar to results for the pooled data analysis.

Conclusions: Despite increased variance, our proposed method offers unbiased estimates and accurate inference. The method can be used in distributed analyses relying on complex drug-outcome models.

260. Choices in Analytically Defining Dichotomous Covariates

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Background: When availability of historical data differs among subjects, investigators might choose between using all available (AA) historical data and considering only data from a collectively shared fixed window (FW) in defining covariates (C). Dichotomous covariates are assumed to be absent unless a claim for the condition is observed. This choice (AA or FW) represents a tradeoff between misclassification and differential ascertainment.

Objectives: To compare bias resulting from the AA vs. FW approach for C ascertainment.

Methods: The effect estimate of interest in this simulation study was the risk ratio representing the effect of a dichotomous exposure (E) on a dichotomous outcome (D) (modeled as RR_{true}), in the presence of a single measured dichotomous C. Across simulations we varied the associations among E, D, C, the time window of available historical data (Coverage), the likelihood of contact with the medical system (Seen), and an unmeasured confounder (U). Subjects were required to have at least 6 months of historical data. Operational values of C were:

C^*_{AA} = C if Seen = 1 and Coverage = 1 in any historical month; =0 otherwise

C^*_{FW} = C if Seen = 1 in historical months -6 to -1 (in whcih Coverage = 1 for all subjects); =0 otherwise

The risk ratio of E on D was estimated using Mantel-Haenszel methods stratified on C^*_{AA} and C^*_{FW} to estimate RR_{AA} and RR_{FW} respectively.

Results: In the base case scenario (RR_{true} = 2; no U), RR_{AA} (2.03; 95% CI 1.89–2.18) was less biased than RR_{FW} (2.14; 95% CI 1.99–2.29); RR_{AA} less biased in 88% of replicates. Differences between RR_{AA} and RR_{FW} (favoring RR_{AA}) were magnified at higher modeled confounder strength, and greater prevalences of C and E. Upon introduction of U, RR_{AA} remained less biased than RR_{FW} except when U had potent and discordant associations with E and D; this pattern was consistent irrespective of effects of U on C, Coverage, and Seen.

Conclusions: In operationally defining time-invariant dichotomous C, the AA approach provides less biased estimates than the FW approach in most instances. Contrary to current practice, investigators should consider defining C based on all available data except in situations where U is anticipated to have potent and discordant effects on E and D.

261. Variance Estimate of Instrumental Variable Two-Stage Logistic Regression Causal Odds Ratio Estimator

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Background: Two-stage logistic regression (2SLR), including two-stage predictor substitution (2SPS) and two-stage residual inclusion (2SRI), is often used in instrumental variable (IV) analysis of binary outcome when there is unmeasured confounding. The 2SPS and 2SRI IV approaches generally involve, as a first stage, the modeling of treatment as a function of the IV and then the second-stage modeling of outcome as some function of predicted treatment or residual from the first stage regression. For either 2SPS or 2SRI approach, the naïve variance estimate obtained from the second stage regression model is not correct, since it does not adjust for the variability of the predicted treatment or residual as a covariate in the second stage regression.

Objectives: We propose adjusted variance estimators of treatment effects estimated by 2SLR. We also evaluate performance of these variance estimators by simulation.

Methods: We use Wooldridge's approach for two-step M estimation to derive the variance estimator of the 2SPS and 2SRI estimators of the log odds ratio. We derive separate objective functions for the first and second stage models from which we obtain separate score and Hessian equations. Then we used the sandwich estimator, which was adjusted for the first-stage regression, to estimate the variances. We use simulation to compare these adjusted variance estimators with the naïve variance estimators as well as with bootstrap estimates of variance.

Results: The adjusted estimators provide approximately unbiased estimates of the true variance but the naïve estimators without the adjustments are biased, and the bias can be as high as 32% under the condition of weak IV. The sandwich estimators of variance we propose are also superior to the bootstrap approach. This study also shows that the 2SRI method has a larger variance than the 2SPS method, which means there is a trade-off between precision and accuracy.

Conclusions: When we use the two-stage logistic regression to do the IV analysis, we have to adjust the variance estimates for the first-stage regression. The sandwich estimators we propose are accurate for both 2SPS and 2SRI approaches.

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262. Sample Size and Serious Adverse Events in Late Phase Comparative Studies

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Background: If a clinical study reports one or more serious adverse events (SAEs) in patients exposed to a sponsor's product but none in patients exposed to a comparator, the result is unfavorable for the sponsor whether or not the difference in SAE rates is statistically significant. This unfavorable outcome can occur by chance, even when the underlying SAE rates are the same in the two treatment groups. For example, if a study has 80% power to detect one or more SAEs in each treatment group, there will be a 1 in 6 (16%) chance of having SAEs in one treatment group and not the other. This paper investigates two strategies for limiting the risk of this unfavorable outcome.

Objectives: To investigate strategies for sample size calculation in comparative studies that record adverse events.

Methods: (1) One strategy is to select sample sizes so that the maximum probability of finding SAEs in one group but not the other is set at a threshold, say 5%. (2) Another strategy is to assign relative values (utilities) to the four possible SAE outcomes, recognizing that the effects of finding SAEs in one group but not the other are not symmetric between groups. Sample sizes are those required for a beneficial expected utility.

Results: (1) If the threshold probability for an unfavorable outcome is set at 5%, and the SAE rate is 1/10,000, then the sample size should be either fewer than 543 or more than 29,415 per treatment group. (2) If utilities are set at -0.3, -1, 0.5, and 0.2 for finding SAEs in (1) both groups, (2) sponsor product only, (3) comparator only, and (4) neither group, respectively, the sample size should be fewer than 2,877 in each treatment group when the SAE rate is 1/10,000.

Conclusions: When designing comparative clinical studies in which SAEs are recorded, consideration should be given to the risk of finding SAEs in patients exposed to the product of interest but not in patients exposed to the comparator when the population event rates are the same. If necessary, sample sizes should be adjusted to minimize this risk.

263. An Efficient and Inexpensive System for the Distribution and Tracking of Investigational Medicinal Products in Streamlined Safety Trials

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Background: Observational studies struggle to detect statistically significant differences where events are rare and relative effect sizes are small. Large scale streamlined trials are increasingly being used to meet post-licensing regulatory requirements to investigate the safety of novel medicines. Such trials confer certain legal requirements together with the need for meticulous record-keeping. Existing pharmacy structures for distributing Investigational Medicinal Product (IMP) are resource intensive and prohibitively expensive for streamlined trial designs.

Objectives: To design and implement a system for electronically managing and tracking IMP for large scale streamlined trials such as the Febuxostat vs. Allopurinol Streamlined Trial (FAST).

Methods: We identified a barcode-based product tracking system as being the most practical approach. Each barcoded packet of IMP is individually tracked following arrival at the dispensary, into the storage facility, through dispensing, checking and supply to the patients, before unused medication is returned to the dispensary for reconciliation and destruction. Electronic records are continuously updated throughout this process. The system incorporates automated checks and automatically generates bespoke medication labels, patient direction leaflets and other paperwork, in either English or Danish, as appropriate for the patient. Technicians assemble distribution packs in one work-stream and then check packs on another work-stream to reduce errors. The system is integrated into the trial electronic Case Report Form (eCRF) from which regimen changes can be made.

Results: We have developed an inexpensive, robust and legally-compliant system of managing supply of medication to study participants. The system is currently being used to manage the drug supply for the FAST trial which can involve a variety of complex medication regimens.

Conclusions: We have produced a semi-automated system for managing drug distribution that reduces cost, minimises errors, provides a robust audit trail and improves the quality and efficiency of drug supply in the clinical trial setting.

264. A Pilot Study to Investigate the Supply of Investigational Medicinal Product to Patients Via Mail in a Streamlined Safety Study

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Background: Large scale streamlined trials are increasingly used to meet post-licensing regulatory requirements to investigate the safety of novel medicines. Existing structures for distributing Investigational Medicinal Product (IMP) are resource intensive and prohibitively expensive for such trials. The Febuxostat vs. Allopurinol Streamlined Trial (FAST) supplies IMP to patients by mail to minimise these costs. To maximise follow-up it is important that patients receive their IMP in a timely manner without inconvenience.

Objectives: To investigate the feasibility of delivering IMP to patients by post.

Methods: Two sizes of specially designed IMP postal-pack were developed to allow 2-month supplies to be made to patients. The pack dimensions were: pack A $30.2 \times 18.9 \times 1.2$ cm; pack B $25.4 \times 20.4 \times 1.6$ cm. Volunteers in this study were drawn from staff at six study centres in the UK. Each participant was mailed 3 combinations of pack A (single, double and triple packs combined) and 2 of pack B (single and double) reflecting the needs of the study. We assessed: (1) proportion of packs delivered via the participants' letterboxes; (2) time to delivery; (3) degree of inconvenience caused when not delivered by letterbox; and (4) extent of damage caused to packs.

Results: Of 270 pack combinations were sent to 54 subjects. Of these, 192 packages (71.1%) were able to be delivered via the letterbox, 61 (22.6%) were delivered by other means and 17 (6.3%) packs went undelivered. The median time to delivery was 1 day. Ninety-five percent of packages were delivered within 5 days. Missed deliveries were assessed as "very inconvenient" in 9 cases (3.3% of total). This would be 9.6% of total including the undelivered packs. Excessive width was the most common reason for packs not fitting letterboxes. Of 44 (18.0%) packages showed some damage: this was all superficial and judged unlikely to affect the integrity of the IMP.

Conclusions: FAST study medication packs could be delivered successfully to 70% of volunteers via letterboxes. Non-delivery of packs resulted in considerable inconvenience in up to 10% of cases. To maximise follow-up amongst FAST patients, the pack widths need to be minimised.

265. Obtaining Risk Ratios from Regression Models: A Cautionary Tale

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Background: Poisson, log-binomial (Lbin), and logistic regression models can be used to estimate cumulative incidence AKA risk ratios (RR). It is known that Log-binomial (Lbin) models may fail to converge and Poisson models may estimate risk in excess of 100%.

Objectives: To evaluate the Lbin, logistic, and Poisson regression models on simulated outcomes created using Framingham Heart Study (FHS) continuous variables as predictors.

Methods: FHS serum glucose data (N = 5,209) were standardized and used as a predictor to simulate dichotomous outcomes in logistic, Poisson and Lbin regression models, with parameters selected to achieve approximately 50% incidence and RR of 1.2 for a 1 SD change in this example. All three analysis models were evaluated as to their ability to correctly estimate the RR of the generating model, agreement among the models as to RR estimates and differences between true and estimated risk (ER). Models were characterized as to sensitivity of RR estimates to outliers in the glucose variables.

Results: Poisson model RRs had the best agreement ($\Delta < 1\%$) with data generated as Lbin or logistic. Lbin and logistic model RRs showed less agreement with other model's data ($\Delta = 7.1\%$ and 1.6%, resp.). Lbin RRs had the greatest sensitivity to outliers even with Lbin data (RR of 1.194 w/out vs. 1.016 with). Poisson models were less sensitive (1.162 vs. 1.098). Logistic models showed no sensitivity to outliers. Poisson ERs often exceeded 100%, deviated up to 40% from truth and were outlier sensitive. Lbin had up to 20% deviations and were outlier sensitive while logistic models had up to 10% deviations and were not sensitive.

Conclusions: With modest effect sizes and 50% incidence, Lbin models, with failures to converge, poor risk estimation and great sensitivity to outliers are a poor tool in modeling risk with continuous predictors. Poisson models were good RR estimators, but ERs >100% and were also sensitive to outliers. Logistic RR estimates had lower bias than Lbin models, estimated risk well and never estimated risk >100%, and all estimates were insensitive to outliers. Poisson modeling requires care with high incidences and predictor outliers, especially when ER is important.

266. An Example in Which Omitting an Instrumental Variable from a Propensity Score Leads to a Biased Estimate of the Effect of an Exposure

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Background: When using regression to control for confounding when estimating the effect of a treatment, controlling for a variable that affects the probability of receiving treatment but not the outcome reduces precision without any benefit in reducing bias. However, propensity methods require that the functional form of the association between a confounder and the treatment be correctly specified.

Objectives: To investigate how controlling for an instrumental variable consisting of the interaction between two

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confounders affects the bias in the estimated treatment effect.

Methods: Two uncorrelated normally distributed variables, X_1 and X_2, were simulated with mean 0 and variance 1. Then a treatment variable, T, was simulated with logodds $(T = 1|X_1, X_2) = X_1 + X_2 + X_1*X_2$. A normally distributed outcome was simulated as $Y = X_1 + X_2 + T + \epsilon$, where ϵ had a normal distribution with mean 0 and variance 1. Samples of size 2,000 were simulated, 1,000 in total. The effect of T was estimated using linear regression models both including and excluding the interaction term X_1*X_2. Propensity scores were also calculated both including and excluding the interaction term, and inverse probability of treatment weighting used to estimate the effect of T.

Results: When using regression to control for confounding, the mean bias in the treatment effect was 0.00 whether the interaction term was included in the regression or not. However, the standard deviation of the estimates was lower when the interaction term was not included (0.048 vs. 0.050). However, when using IPTW to control for confounding, omitting the instrumental interaction led to biased estimates of the treatment effect (mean bias -0.36, SD 0.18). The bias when the interaction term was included was reduced to 0.02 (SD 0.19).

Conclusions: When an interaction between two confounders affects the probability of receiving treatment but not the outcome, and regression is used to control for confounding, the interaction term should not be controlled for. On the other hand, there are situations in which omitting an instrumental variable from a propensity score model will lead to the introduction of bias.

267. Assessing Therapies in Rare Disease Patients: Re-Evaluating the N-of-One Crossover Design

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Background: Designing studies to assess drug effect in rare disease population is challenging, hence innovative designs to obtain maximum information by comparison within patients is desirable.

Objectives: To propose an innovative use of the n-of-one crossover design applied to study populations which allows estimation of instant and cumulative drug effects on rare diseases, and to explore its connection to the pharmacological mechanism via an effect-compartment model.

Methods: We propose n-of-one crossover designs with a rich pattern of treatment variation yet preserving certain properties of optimal crossover designs. Acute effects of treatments are found by the mean of the difference in response between active treatment and placebo or active treatment and comparator. Cumulative treatment effects (representing chronic or disease modifying effects) are assessed using time-dependent carry over effects that will likely increase after each active treatment and decrease after placebo or comparator. The design principle can be used for other diseases and treatments with rapid or slow onset and weak or strong carry-over effects or disease modification effects. Optimal design approaches can be used to determine treatment allocation and sampling time based on a drug's pharmacological characteristics. With the designs, we model carry-over effects either empirically or by using the effect compartment model. Performance of the designs has been evaluated by simulations.

Results: Designs with satisfactory performance and certain optimal properties were obtained. Using a simulation approach, we show significant benefit of the design over the traditional parallel group designs, whether using the empirical or model based estimation of instant and cumulative treatment effects. Based on the estimation, impacts of dosing pattern change and non-compliance were also evaluated, showing flexibility of using the designs to answer relevant clinical questions.

Conclusions: Appropriate use of crossover design for rare diseases has clear advantage over traditional parallel designs. Research on design and analysis methodology will further strengthen the approach and facilitate its implement in practice.

268. Characterization of Missing Data in Clinical Registry Studies: Study Design and Methods

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Background: Missing information is a common and important problem in epidemiology. However, missing data have not been well-characterized in observational research studies.

Objectives: To systematically characterize and identify predictors of missing data in real-world registry-based studies.

Methods: We are evaluating existing data from diverse registries selected from different therapeutic and disease areas, and with different focus (e.g., product, disease) and sponsor type (e.g., commercial, medical association). Three data sources will be utilized: a rare disease registry, a registry addressing comparative effectiveness of treatments for an ophthalmologic condition, and a large procedure registry in a surgical specialty area. Data sources include medical record and health-care professional-reported data, as well as patient-reported clinical and quality of life outcomes. The proportion of missing data for variables representative of the following domains will be described: demographics, medical history and disease

severity, treatment status, and patient-reported outcomes. Generalized linear mixed effects models, accounting for within patient and/or within site correlation, will be employed to identify factors that are independently associated with specific missing data elements in each registry. Principles of the method described by Potthoff et al. will also be employed to test whether missing data is consistent with the assumptions of MAR+.

Results: Preliminary data analysis including over 1,800 patients for the ophthalmologic disease registry indicates that the proportion of missing information for baseline demographic variables age, gender, and race were minimal (<1%). An index of disease severity was missing in <10% of patients.

Conclusions: The current project will contribute to the knowledge gap in the field of missing data in non-randomized comparative effectiveness research and will inform the use of appropriate analytic methods to account for missing information.

269. What's on Your Reference Shelf? A Guide to Essential Pharmacoepidemiologic Guidances

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Background: Pharmacoepidemiologists responsible for the design, analysis, and reporting of observational studies are not permitted the luxury of focusing solely on matters of science. Changing regulations and advancing technologies mean that the pharmacoepidemiologist must be prepared to function in a much broader context throughout a study's conduct. Pharmacoepidemiologists working at contract research organizations (CROs), for example, may be asked to opine on matters concerning the need for: adverse event reporting, informed consent, 21 CRF Part 11 compliance, percentage of source data verification needed, etc.

Objectives: There are numerous and very robust guidances (principles or statements) available for the practicing pharmacoepidemiologist. They include the: Guidelines for Good Pharmacoepidemiology Practices; GRACE Principles; *Registries* for Evaluating Patient Outcomes: A User's *Guide; STROBE Statement; FDA* Guidance for Industry on Patient-Reported Outcome Measures; and so on.

Methods: We characterized the guidances by their content and focus, authorship/sponsorship, as well as age and access. We included a list of frequently asked questions (FAQs) in observational study research for which one or more of the guidances might be consulted. Finally, we identified those FAQs for which guidance is currently and notably absent.

Results: We created a compendium of these essential guidances along with a "What to Consult When" table for the potentially overwhelmed pharmacoepidemiologist.

Conclusions: We intend to maintain for our own use – and for our colleagues' use around the globe – a published, dynamic compendium which can be updated as new guidances are written and older guidances are updated.

270. Comparison of Interaction and Subgroup Effects in Observational Studies and Randomized Clinical Trials: Three Empirical Examples

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Background: Compared to RCTs, observational (non-randomized) studies often comprise larger sample sizes, which gives adequate power to study interaction. Observational studies, however, are prone to confounding.

Objectives: To determine the validity of subgroup and interaction effects (differences between subgroups) for different study designs.

Methods: We compared effects of medical interventions based on observational studies, RCTs, and Individual Patient Data Meta-Analysis of RCTs (IPDMAs; reference) on three different clinical topics: (1) mammography screening effects on breast cancer mortality; (2) CABG and all-cause mortality; (3) statins and the incidence of major coronary events. Main, subgroup, and interaction effects were compared.

Results: Main and subgroup effects were comparable with respect to the direction of effects for IPDMAs, RCTs, and observational studies. Small differences in the magnitude of subgroup effects in observational studies yielded different interactions compared to IPDMA. In the mammography example the Ratio of Risk Ratio's (RRR) (i.e., interaction effect) among observational studies was 1.46 (95% CI 1.09;1.96) compared to an IPDMA effect of 1.10 (95% CI 0.89;1.37). For the CABG studies the observational RRR was 1.03 (95% CI 0.84;1.26), whereas in the IPDMA this was 1.40 (95% CI 1.08;1.1.81). Finally, in the statin example the RRR was 1.35 (95% CI 1.13;1.61) for observational studies, in the IPDMA this was 0.90 (95% CI 0.84;0.97).

Conclusions: Main and subgroup effects based on observational data are in line with main and subgroup effects in IPDMAs based on RCTs, yet interactions may differ substantially.

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271. Influence of Time-Varying Prognosis in Self-Controlled Analyses

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Background: Self-controlled analysis methods implicitly adjust for time invariant confounding within individuals. In practice, individuals' prognoses can vary over time and affect drug use and subsequent health outcomes; healthy patients frequently initiate preventive medications whereas moribund patients discontinue them.

Objectives: To evaluate the potential impact of healthy-user/sick-stopper biases in the self-controlled setting and the extent to which alternative adjustment strategies could mitigate these biases.

Methods: We used Medicare data to conducte case-crossover (CC) studies of the short-term relation between five classes of preventive medications intended for chronic use (statins, oral hypoglycemics, antihypertensives, osteoporosis and glaucoma medications) and death. We evaluated the ability of the case-time control (CTC) and case-case time-control (CCTC) to adjust for exposure-time trends induced by healthy-user and sick-stopper biases. The CTC estimates the time trends through a crossover analysis of the exposure of interest in a sample of controls while the CCTC uses a crossover analysis of control drugs among the sample of cases.

Results: The CC odds ratios were 0.38, 0.38, 0.40, 0.39, and 0.50, for statin, hypoglycemic, antihypertensive, osteoporosis, and glaucoma drugs, respectively; naively suggesting that initiation of preventive medicines had an immediate implausible protective effect on mortality. Adjusting for exposure-time trends measured among matched controls (CTC) did not materially change these estimates (0.54, 0.51, 0.54, 0.37, and 0.54), however after adjusting for exposure-time trends using control drugs measured among the cases (CCTC), the majority of estimates clustered around null (0.90, .92, 0.97, .94, and 1.29).

Conclusions: Careful consideration of the sociology of medication use – for instance, whether use at a particular time but not at another is associated with prognosis – is essential in designing and analyzing drug safety studies. The CCTC may be used to adjust for strong time-varying confounding, such as that due to healthy-user and sick-stopper biases.

272. Media Campaign for Recruitment to a Streamlined Safety Trial in Scotland

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Background: Engaging patients is a major hurdle in clinical studies. Advertisements in local and national newspapers may improve public awareness and subsequently improve the recruitment rate in clinical studies.

Objectives: To describe the general population response to the SCOT trial (Standard card vs. Celecoxib Outcome Trial) advertisements in local and national newspapers.

Methods: Between July 2009 and March 2010, 6-day advertisements for the SCOT trial appeared in 4 local newspapers and 6 national newspapers across Scotland. Advert responses by telephone were recorded by research nurses from the SCOT trial.

Results: The newspapers have wide coverage across Scotland. Two of the newspapers -The Daily Record and Sunday Mail – reach 32% of Scottish adults (the total population of Scotland was 5,222,100 according to June 2010 estimates) and the circulation of these two newspapers are over 600,000. The total cost for advertisements was £45,044. However, only 319 people responded to the advertisements by phoning the SCOT trial help line with 47% (n = 149) responding to the advertisement in local newspapers and 53% (n = 170) in national newspapers. The proportions of people responding from different areas were 32% from Glasgow, 17% from Edinburgh, 9% from Aberdeen, 8% from Dundee, 7% from Fife and 27% from the rest of Scotland. Of all the subjects who responded 52.3% were "suitable."

Conclusions: Advertisements in local and national newspapers are costly and largely ineffective, attracting only small numbers of respondents.

273. The Role of PS Estimation and Implementation in the Presence of Heterogeneous Effects of Covariates on Treatment

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Background: The impact of propensity score (PS) model misspecification that results from omitting interaction terms which affect treatment, but not outcome, is not well understood. Such situations are likely to occur e.g., when indications for treatment assignment vary over calendar time. In these situations, calendar time might be thought of as an instrumental variable interacting with a given set of indications for treatment.

Objectives: We evaluated the potential for misspecified PS models, which result from omitting interaction terms

which affect treatment but not outcome, to result in valid treatment effect estimates.

Methods: Simulations consisted of a dichotomous treatment (T), Poisson outcome (Y), two confounders (X_1, X_2), and an instrumental variable (X_3). Simulations were performed with both dichotomous and continuous predictors of treatment (X_1 - X_3). Interactions were included in the treatment model one at a time and the strength of each interaction term was varied while holding all other terms constant. PSs were estimated using logistic regression models which included only main effects of the confounders (X_1, X_2). PSs were implemented using inverse probability treatment weighting (IPTW) and matching.

Results: For scenarios with continuous predictors of treatment, the percentage bias ranged from 4% to 61% for IPTW and 5–57% for matching when interactions consisted of two confounders, while the percentage bias ranged from 1% to 20% for IPTW and 1–8% for matching when interactions consisted of a confounder and the instrument. When predictors of treatment were dichotomous, effect estimates were biased only when the excluded interaction consisted of two confounders and the PSs were implemented using IPTW (percentage bias ranging from 1% to 8%).

Conclusions: The omittance of interaction terms in PS models generally, but not always, leads to bias. These results imply that if indications for treatment vary over calendar time, it is necessary, in general, to account for the heterogeneous effects of the indications on treatment through modeling interaction terms in the PS model or estimating time-stratified PSs.

274. Estimated vs. True PSs for Controlling Baseline Covariates in RCTs

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Background: Using estimates of the propensity score (PS), as opposed to the true PS values, reduces the variation of effect estimates. However, the amount of variance reduction is unclear and is likely to depend on a variety of factors. This issue is relevant in experimental settings where estimated PSs can be used to adjust for baseline covariates and the unadjusted model is equivalent to using the true PS values. Further, when the outcome model is non-linear, controlling for baseline covariates can change the interpretation of effect estimates.

Objectives: We explored the impact of using the estimated PS to control for baseline covariates on the precision and interpretation of effect estimates in experimental settings.

Methods: We simulated a randomized dichotomous treatment, a normally distributed risk factor, and a single outcome for sample sizes N = 50, 100, 1,000. We replicated each simulation with normally and binomially distributed outcomes while varying the strength of the risk factor-outcome association. The PS was estimated using logistic regression and implemented using IPTW and matching. The treatment effect was also estimated using multivariable regression and the usual, unadjusted outcome model.

Results: The increase in precision of the effect estimate due to control for the estimated PS was proportional to the strength of the risk factor-outcome association. For a normal outcome, the percent variance reduction ranged from 1% to 8% for IPTW and 1% to 11% for PS matching. When the outcome followed a binomial distribution, the percent variance reduction increased slightly for strong risk factor-outcome associations but remained small at $<2\%$ for all scenarios. Controlling for the risk factor using IPTW resulted in an unbiased estimate of the marginal treatment effect.

Conclusions: The estimated PS reduces chance imbalances in risk factors and thus variability of estimates. The magnitude of the variance reduction is dependent on the strength of covariate-outcome associations and the distribution of the outcome. Using estimated PSs to control for baseline covariates through IPTW yields a marginal or population averaged effect estimate directly comparable to the crude randomized estimate.

275. Descriptive Cohort Study of Antibiotic Prescription to the Swedish Children Born in 2006

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Background: Prudent use of antibiotics is important to reduce antibiotic resistance. Careful surveillances of antibiotic consumption with the aim to improve rational use is therefore of great importance. In the database normally used to analyze antibiotic consumption, age is calculated as year of birth minus year of dispensation, thus introducing a misleading age categorization among infants. As a consequence antibiotic prescription patterns in relation to age in infancy are poorly understood.

Objectives: To analyze data on an individual level in order to describe the patterns of antibiotic use in young children in Sweden.

Methods: We analyzed the antibiotic sales data from the Swedish Prescribed Drug Register for each child born in 2006 up to an age of 5 years.

Results: The prevalence of antibiotic prescriptions to young children is highest at 19–21 months age. During

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the first year or life 30% of the Swedish children (n = 30,594/101,555) get at least one prescription of antibiotics dispensed, and almost half of them (13%) more than one prescription. More than one prescription per year are most frequent among children 2 years of age.

Boys are prescribed more antibiotics during their first three living years, while girls are prescribed more antibiotics commonly used to treat urinary tract infections.
Conclusions: Children 1–5 years of age are prescribed most antibiotics between the ages of 19–21 month. More than one prescription per year are common in all age-groups.

276. Antibiotic Prescriptions in Outpatient Children: A Multiregional Comparison

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Background: Antibiotics are the most frequently prescribed drugs in children. Quantitative and qualitative differences in antibiotic prescriptions were found between and within countries.

Objectives: To evaluate paediatric antibiotic prescription patterns in Italy in an out-hospital setting at the regional, Local Health Unit (LHU), and district levels.

Methods: Data sources were regional prescription databases. The study population included all the resident outpatient population <18 years old in three large regions in the North (Lombardy), Centre (Lazio), and South (Puglia) of Italy. The observation period was the year 2008. Prevalence and prescription rates were retrieved at the single LHU and the district levels and the coefficient of variation was calculated for each region. A spearman rank correlation test was performed between prevalence rates and latitude, hospitalization rate, and paediatrician per 1,000 resident children for each district.

Results: The antibiotic prevalence rate was, on average, 47.9%, ranging from 43.1% in Lombardy to 57.5% in Puglia. At the LHU level it ranged from 35.9% to 63.4% and at the district level it ranged from 34.0% to 67.9%. The coefficient of variation ranged from 0.08 in Puglia to 0.13 in Lazio. In Lombardy the percentage of children treated with amoxicillin was twofold higher than in Puglia and Lazio. In a similar way in the central and southern regions a greater use of second choice drugs (cephalosporins and macrolides) was observed. No correlation was found between prevalence rate, paediatricians per 1,000 resident children, and hospitalization rate. There was an inverse correlation between prevalence rate and latitude (rs = -0.71 p < 0.0001).

Conclusions: Relevant differences exist between the northern and the southern part of the country, and that heterogeneity increases when looking into LHUs and districts. The central and southern regions revealed a higher prevalence of antibiotics, a substantially lower use of amoxicillin, and a higher use of second choice treatment.

277. Antibiotic Use in Children and the Use of Medicines by Parents

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Background: Antibiotic drugs are frequently used for viral infections by children. It is probable that health beliefs and solicitudes of parents have great influence on the use of drugs in children.

Objectives: In this study we investigated whether the use of antibiotics in children is associated with the drug use of their parents.

Methods:

Design: An observational cohort-study, following children 0–4 years old and their parents.

Setting: We used the database IADB.nl, containing pharmacy-data from the Netherlands.

Exposures: We selected children who did not use antibiotics till their fifth birthday and a group of children, who obtained at least one antibiotic prescription in every year. Of these two groups we selected the parents.

Main outcome measures: We compared the two groups of parents to each other in regard to the use of antibiotic and other medication. The percentages of users of antibiotic drugs and chronic medication of parents were calculated and also the relative risks of using different groups of medication.

Statistic analysis: To compare percentages, the chi-square test was used. To compare the medication use relative risks (RR) with confidence intervals were calculated.

Results: Parents of children, who used antibiotics recurrently, use more antibiotics recurrently themselves compared to parents of children who did not use antibiotics (mothers: 19.1 vs. 5.5% [p < 0.001]; fathers: 9.1% vs. 3.3% [p < 0.001]). Moreover, this group also shows a higher percentage of chronic medication use: (11.3 vs. 6.2% (mothers, p < 0,001) and 13.1% vs. 9.5% (fathers, p < 0,001). Mothers more often use, among others, NSAIDs (RR: 21/1,234/22/5,790 = 4.7 [2.6–8.6]), analgesics (RR: 17/1,234/24/5,790 = 3.3 [1.8–6.2]) and anxiolytics (RR: 14/1,234/27/5,790 = 2.4 [1.3–4.6]). Fathers use more antacids (RR: 30/1,032/68/4,250 = 1.8 [1.2–2.7]), and NSAIDs (RR: 15/1,032/32/4,250 = 1.9 [1.0–3.5]).

Conclusions: Parents of children, especially mothers, who use antibiotic drugs recurrently, use more medication

compared to the parents of children who use no antibiotic drugs. Parents' medication use may influence the medication use of children and is a factor, physicians and pharmacists should take into account.

278. Antibiotic Prescription Rates in Paediatric Populations of 5 European Countries: A Drug Utilization Study from the ARITMO Project

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Background: The primary objective of the ARITMO project is to analyze the ventricular arrhythmogenic potential of antiinfectives, antihistamines, antipsychotics. Formerly published studies revealed substantial variations in exposure/utilization patterns across European countries, which have to be taken into account in the conduct of drug safety analyses, with respect to power considerations.

Objectives: To describe utilization of antibiotics in children across five different European countries.

Methods: Outpatient prescriptions of antibiotics to children were analysed using data from General Practice (Health Search, CSD LPD; THIN) and record linkage databases (Emilia Romagna Database (ERD); PHARMO; Aarhus; GEPARD) with a target population of around 27 million patients from EU. Antibiotic prescription rates were calculated per 1,000 person years (PY) for each database and stratified by age (0–4, 5–9, 10–14, 15–18 years).

Results: Overall antibiotic prescription rates per 1,000 PY varied by a factor of 3.45 between the country with the highest (992 in Italy, Emilia Romagna) and the country with the lowest (297 in the Netherlands) use. In all countries prescription rates were highest among children in the age group 0–4 years. The majority of prescribed antibiotics in all jurisdictions were penicillins. In the Netherlands, Italy, Denmark and the UK macrolides were second most prescribed, whereas cephalosporins were second most prescribed in Germany.

Conclusions: Antibiotic prescription rates in these 5 countries, support findings of former studies regarding substantial differences in paediatric antibiotic use across Europe. Results of drug utilization analysis will assist researchers in the ARITMO project to identify drugs that yield sufficient power for the assessment of arrhythmogenic risk and the public health impact and to identify differences in risk due to cross-country variability of use.

279. Antiviral Prescription Rates in Paediatric Populations of 5 European Countries: A Drug Utilization Study from the ARITMO Project

Jakob Holstiege,[1] Tania Schink,[1] Giampiero Mazzaglia,[2,3] Gianluca Trifirò,[4,5] Francesco Innocenti,[2,3] Alessandro Oteri,[4,5] Ron Herings,[6] Irene Bezemer,[6] Elisabetta Poluzzi,[7] Aurora Puccini,[7] Sinna Pilgaard Ulrichsen,[8] Lars Pedersen,[8] Miriam C Sturkenboom,[5] Edeltraut Garbe.[1] *[1]Institute for Epidemiology and Prevention Research, Bremen, Deutschland, Germany; [2]Health Search Italian College of General Practitioners, Florence, Italy; [3]Regional Agency for Healthcare Services of Tuscany, Florence, Italy; [4]Department of Medicine and Pharmacology, University of Messina, Messina, Italy; [5]Department of Epidemiology and Biostatistics and Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [6]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [7]Department of Pharmacology, University of Bologna, Bologna, Italy; [8]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: The EU-funded ARITMO project aims to assess the utilization and the arrythmogenic potential of antiinfectives, antihistamines and antipsychotics. A recently published study reported considerable differences in overall utilization of antiviral medications across Europe, however without distinguishing between different age groups. To our knowledge no study has assessed antiviral drug use in children up to now.

Objectives: To describe outpatient utilization of antivirals in children across Europe.

Methods: Outpatient prescriptions of antivirals to children were analysed using data from General Practice (Health Search, CSD LPD; THIN) and record linkage databases (Emilia Romagna Database (ERD); PHARMO; Aarhus; GEPARD) with a target population of around 27 million persons from EU. Antiviral prescription rates were calculated per 1,000 person years for each database and stratified by age (0–4, 5–9, 10–14, 15–18 years) using a standardized Jerboa software.

Results: Overall antiviral prescription rates varied by a factor of 4.7 between the country with the highest (10.5 in Italy, ERD) and the country with the lowest (2.2 in the Netherlands) rates. Rates in Denmark, the Netherlands, Germany, and the UK were highest in the age group 15–18 years, whereas in Italy (ERD) most prescriptions were issued to children in the age group 0–4 years. The majority of prescribed antivirals in all jurisdictions were nucleo-

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sides and nucleotides excl. reverse transcriptase inhibitors, followed by neuraminidase inhibitors. Monthly prescription rates showed sporadic pronounced peaks, most likely associated with regional influenza outbreaks, suggested by increased prescriptions of neuraminidase inhibitors during these peaks.

Conclusions: Exposure of children to antiviral medications varies substantially between European countries. In accordance with the expected indications of antiviral use in children as e.g., herpes and influenza, the most frequently prescribed antivirals were aciclovir and neuraminidase inhibitors.

280. Abstract withdrawn by author.

281. Paediatric Oseltamivir Prescriptions in Primary Care in United Kingdom, Italy and Netherlands during the 2009 A/H1N1 Pandemic

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Background: Oseltamivir is indicated in patients 1 year of age and older who present with symptoms typical of influenza. During the 2009 A/H1N1 pandemic outbreak, oseltamivir was also indicated for the treatment of infants below 12 months of age. This implied that oseltamivir was used for the first time on a large scale in infants since its registration in 2005.

Objectives: In this study we aimed to describe the prescription pattern of oseltamivir to children in primary care in the United Kingdom (UK), Italy (IT) and the Netherlands (NL) in 2009.

Methods: We conducted a retrospective cohort-study in three electronic medical records databases; The Health Improvement Network (THIN) (UK), Pedianet (IT), and Integrated Primary Care Information (IPCI) (NL) and included all children and adolescents (0–18 years) with a total of 27,560,565 person-months (PM) of follow-up in 2009. Monthly prevalence of oseltamivir prescriptions was calculated for 2009; defined as the number of children with at least one prescription per month per 1000 PM.

Results: The monthly prevalence of oseltamivir prescriptions showed a biphasal pattern in NL and UK with a first peak in July and a second peak in October/November.

In line with the number of influenza-like-illness cases reported to ECDC in this period, the peak in prescriptions was most prominent in July (6.6 users/1000 PM) in the UK and in November (1.5 users/1000 PM) in NL. The prevalence in Italy was limited (max. 0.2 users/1000 PM) and no seasonal trend was evident. Within age-categories, the monthly prevalence was highest for children aged 1–5 years (NL: 2.6/1000 PM in November; UK: 10.7/1000 PM in July). For infants <1 years, the prevalence was max. 2.1/1000 PM in NL, 5.7/1000 PM in UK and 0.3/1000 PM in IT.

Conclusions: During the 2009 pandemic, oseltamivir prescriptions peaked in July in UK and in November in Netherlands, with a high prevalence in infants <1 year of age. The high peak in the UK may reflect changes in prescribing policy at this time. The variation in prescribing rates across Europe suggests inconsistency in the indications for oseltamivir in children.

282. Abstract withdrawn by author.

283. Topical Use of Corticosteroids among Children and Adolescents with Atopic Dermatitis in Germany

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Background: Atopic dermatitis is a chronic relapse skin disorder affecting 10–20% of children in industrialized countries. Topical use of corticosteroids has been considered the standard treatment for atopic dermatitis. Parents tend to oppose the use of corticosteroids in their children fear of side effects.

Objectives: To investigate the use pattern and users' profiles of topical corticosteroids among children in Germany.

Methods: German Health Interview and Examination Survey for Children and Adolescents (KiGGS) 2003–2006 recruited a national community sample of 17,641 children and adolescents aged 0–17 years. Atopic dermatitis in the last 4 weeks and topical use of corticosteroids in the last 7 days prior to the medical interview were investigated among all study children by health professionals.

Results: Of 271 corticosteroids-containing preparations were used by 259 children. An overall users' prevalence was 1.32% (95% confidence interval 1.11–1.57%) in the general child population and 12.8% (10.3–15.8%) among children reporting atopic dermatitis in the last 4 weeks. Corticosteroids of group III (potent) were the most frequently used (49.1%), followed by group I (weak, 26%) and group II (moderately potent, 13.7%). Corticosteroids of group IV (very potent) were little used (0.4%). Among children with atopic dermatitis in the last 4 weeks, use of corticosteroids showed no significant difference in the subgroups stratified by socio-demographic, socioeconomic and health-related behaviour factors, either in the bivari-

ate or multivariable logistic analyses, except for children residing in the eastern part of Germany (adjusted odds ratio 2.07, 95% CI 1.20–3.57), in spite of the significantly higher prevalence rates of atopic dermatitis found in these subgroups.

Conclusions: Topical use of corticosteroids appears to be low overall among children with atopic dermatitis in Germany. Although atopic dermatitis is associated with children from families of higher socioeconomic status, topical use of corticosteroids among children with atopic dermatitis does not show significant differences in terms of socioeconomic background. The underlying reasons remain subject of further investigations.

284. Utilization of Antidiabetic Drugs among U.S. Children and Adolescents, 2002–2011

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Background: The prevalence of diabetes mellitus among pediatric patients in the U.S. has been increasing, especially rates of type-2 diabetes mellitus in adolescents. New pharmacologic treatment options have become available during the last decade.

Objectives: To describe antidiabetic drug (AD) use in the U.S. pediatric population, including age at initiation.

Methods: We queried the IMS Health, Vector One® National and Total Patient Tracker databases for prescription (Rx) AD use in the U.S. pediatric population (≤19 years) for the years 2002–2011. Data are nationally projected based on retail pharmacy Rx activity. Initial therapy was defined as an AD Rx preceded by 12 months of no use of any AD. No statistical tests were performed.

Results: In year 2002, 283,580 pediatric patients received 1.8 million AD Rxs, reflecting 1.7% of the total AD market. In year 2011, 443,194 pediatric patients (56.3% increase from year 2002) received 2.3 M AD Rxs (31.5% increase) reflecting 1.5% of the total AD market by Rxs. Sixty percent of newly initiated AD therapy in 2011 was insulin (mean age at initiation, 11.4 years; range: 9.2 years, insulin nph human recom to 15.5 years, insulin npl/lispro). In year 2002, 24.8% of all pediatric AD recipients were prescribed non-insulin (NI) ADs and 27.0% in year 2011. Initiators of NIADs had a mean age of 15.3 years (range: 10.5 years, glipizide to 17.1 years, pramlintide). The most common initial NIAD therapy in year 2011 was metformin (89.1% of initial NIAD Rxs), followed by glipizide (4.4%). Similarly, single ingredient (SI) metformin (86.4% of NIAD Rxs) and SI glipizide (5.6%) were the most commonly dispensed NIAD Rxs in 2011. Two newer classes, DPP-4 inhibitors and daily injectable GLP-1 analogs, represented 1.3% and 1.2% of all pediatric NIAD Rxs, respectively.

Conclusions: A minority of pediatric AD recipients used NIADs. NIAD initiators were older than insulin initiators, reflecting the predominance of type-1 diabetes mellitus among children. The increase in AD recipients outpaced pediatric population growth in a similar time period (2002–2010: 2.5% increase). Metformin and sulfonylureas were the most commonly used NIADs; there was little use of two new AD classes.

285. Aminoglycoside Eardrops and Risk of Sensorineural Hearing Loss in Children with Non-Intact Tympanic Membranes

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Background: Topical antimicrobial therapy is commonly used to treat otitis media with a non-intact tympanic membrane (NITM), due to perforation (TMP) or tympanostomy tube (TT). Fluoroquinolone use has been promoted over aminoglycosides in such cases, because of the risk of ototoxicity. No large scale study has examined the risk of ototoxicity with topical aminoglycoside therapy in NITM.

Objectives: To evaluate the comparative safety of neomycin and quinolone eardrops in terms of risk of sensorineural hearing loss (SNHL).

Methods: This was a retrospective cohort study of 29 states Medicaid beneficiaries eligible between 1999 and 2006. Patients were enrolled if they were < 18 years and had 1 claim for TMP or TT, had 1 dispensing of a study eardrop within 12 months after TMP or TT, and were continuously enrolled in Medicaid at least 6 months before and 12 months after their first eligible dispensing. Patients with history of organ transplant, rubella, and syphilis, and other high-risk conditions were excluded. We compared the 12 month risk of incident SNHL using Cox proportional hazards regression models adjusting for demographic variables, days between surgery and antibiotics initiation, TMP vs. TT, total number of otic claims during follow up, and other risk factors of SNHL.

Results: Among 135,057 children treated with neomycin or quinolone eardrops, 1,747 cases of SNHL were found. Compared to fluoroquinolone use, the adjusted hazard ratio (HR) for 1st, 2nd, and ≥3 prescriptions of neomycin was 1.01 (95% CI: 0.89, 1.14), 1.32 (95% CI: 1.03–1.68), and 1.32 (95% CI: 0.86, 2.02) respectively. When we restricted the population to patients with NITM due to TT, the HR was 1.06 (95% CI: 0.92, 1.22) and 1.41 (95% CI: 1.10, 1.82) for 1st and ≥2 prescriptions of neomycin, compared to fluoroquinolone use.

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Conclusions: Short-term use of neomycin ear drops in patients with NITMs does not carry a significant risk of SNHL compared quinolone eardrops. Repeated doses of topical neomycin are associated with an increased SNHL risk.

286. Monitoring of DMARDs Safety in Children with JIA in Crimea

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Background: Juvenile idiopathic arthritis (JIA) is one of the leading reasons of social activity decrease in childhood and further loss of work ability. Aggressive therapy of JIA is additional factor of risk due to high frequency of adverse reactions (ADR).

Objectives: To increase safety of disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), sulphasalazine (SSZ), cyclosporine A (CSA), azathioprine (AZT) and combination of methotrexate and glucocorticoids (MTX + GC) in patients with JIA according to data of ADR monitoring.

Methods: Ultrasound density, markers of bone remodelling (osteocalcin and deoxypiridinoline), calcium and phosphorus, markers of inflammation (haptoglobin, CRP, seromucoids, leucocytes and ESR) in correlation with pharmacotherapy data (dose, duration of therapy) were studied in 153 patients in Republic Pediatric Hospital during 3 years.

Results: We found correlation of calcium levels and ultrasound densitometry data (ρ = -0.805, $p < 0.05$), increased risk of osteopenia in all groups excluding MTX and SSZ ones, dependence of bone density on dose (MTX + GC) and therapy duration (AZT), dependence of synthesis marker (osteocalcin) on doses in MTX + GC (ρ = -0.502), CSA (ρ = -0.739) and AZT (ρ = -0.933) groups and correlation of resorption marker with densitometry data in MTX groups and CSA patients (r = -0.779). Most apparent inhibition of rate of growth was found in AZT patients while SSZ did not inhibit growth rate. In all groups excluding MTX and SSZ processes of weight, stature and BMI inhibition were dose-dependent and in AZT patients additionally duration-dependent. During monitoring next ADR were also registered: anemia (MTX – 14.8% of patients, MTX + GC – 33.3%, AZT – 70%), leucopenia (SSZ – 6.38%; MTX – 15.78%), severe thrombocytopenia (AZT – 1 case). No pathological changes in liver and kidney functions were found.

Conclusions: DMARDs except MTX and SSZ influence on correlation and the dose/duration dependent increase of risk of osteopenia, growth, and weight and BMI retardation. The most negative influence on studied parameters was found in AZT group. We found the mentioned ADR had not been included in short medicinal product characteristics (SMPC), thus, SMPCs should be updated.

287. A Cross-Sectional Study on Patient Treated with Anti Epileptic Drugs

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Background: There are many studies regarding monotherapy and polytherapy of AED's, only limited studies discussed the impact of Adverse Drug Reactions (ADR's) and depression among patients with AED's.

Objectives: The primary objective is to study the ADR's profile of patients treated with AED's (monotherapy-single drug and polytherapy-more the one) and to assess whether depression may aggravate the number and intensity of ADR's among patients with AED's.

Methods:

Design: A prospective observational study was conducted over 6 months from June 2009 to December 2009. About 91 patients treated with monotherapy and polytherapy were included in the study and ADR's were monitored during first and second visits. A detailed semi structure and CES –D questionnaire was used to study the depression and its impact on ADS's.

Setting: The study was conducted in the outpatient department of epilepsy clinic, at Coimbatore. Irrespective of Genders were included in the study, those prescribed for at least 6 months and on stable dose for at least 3 months of AED's. Exclusion criteria include patients below 18 years, non compliant patients, with febrile illness, cognitive impairment and those with uncertain diagnosis of epilepsy.

Exposures/interventions: Patients were treated with Phenobarbital, Phenytoin, Carbamazepine, Valproate, Lamotrigine, Gabapentin, Tigabine, Topiramate, Levetiracetam, Oxcarbazepine, Clobazam, Pregabalin and Zonosamide.

Main outcome measures: To study the incidence and intensity of ADRs on AED pharmacotherapy and its relationship with depression.

Statistical analysis: Used Mann–Whitney U-test, Kruskal–Wallis test and Wilcoxan signed rank test.

Results: Incidence of ADRs in patients those who received monotherapy (49) and polytherapy (42) $p = 0.784$ was not greatly varied and also shows the same in increase of an ADR between the patients with depres-

sion and without depression. But there was a significant difference in the depression level among patients with mono and poly therapy ($p < 0.001$).

Conclusions: Incidence of ADRs and its intensity has no relationship with respect to gender, age, therapy and level of depression whereas level of depression associates with therapy.

288. Second Generation Antipsychotics and Risk of Type 2 Diabetes in Publicly Insured Children and Adolescents

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Background: Use of second generation antipsychotics (SGAs) in youth has increased substantially despite concerns about adverse cardiometabolic effects.

Objectives: This study aims to estimate the comparative risk for incident type 2 diabetes for individual SGAs in publicly insured 6–24 year-olds.

Methods: The study used Medicaid Analytic Extract data from 45 States (2001–2005), representing more than 95% of Medicaid-eligible youth with fee-for-service coverage in the US. We conducted a retrospective cohort study in 161,559 youth newly started on risperidone, quetiapine, olanzapine, aripiprazole, or ziprasidone. New SGA treatment episodes required 365 days of eligibility without claims for any antipsychotic. Patients were excluded for serious general medical illnesses, pregnancy, polycystic ovarian syndrome or evidence of diabetes prior to the index date. Study outcome was incident type 2 diabetes defined by a claims-based algorithm validated against medical records (PPV = 89.1%). Cox proportional hazards models assessed type 2 diabetes risk of individual SGAs compared to risperidone (referent). Follow-up began at date of first SGA claim and was censored at study outcome, SGA discontinuation, SGA switch/addition, age 25, end of study period, loss of eligibility or death, whichever came first. Propensity scores (PSs) were used to adjust for a broad set of claims-based covariates assessed during the 365-day pre-index period.

Results: We observed 289 cases of incident type 2 diabetes during 55,140 person years of follow-up. Mean time to censoring was 125 days (median 73 days). Treatment discontinuation was the predominant censoring reason. PS-adjusted models showed no significant differences of any SGA compared to risperidone (quetiapine, HR 1.13 [0.81–1.57]; olanzapine HR 1.31 [0.93–1.85]; aripiprazole HR 1.35 [0.89–2.06]; ziprasidone HR 1.44 [0.75–2.79]).

Conclusions: We observed no differences in type 2 diabetes risk between individual SGAs. Failure to detect such differences may be due to residual confounding from channeling of high risk patients to SGAs perceived to have less metabolic adverse effects and/or short follow-up resulting from early SGA discontinuation.

289. A Population-Based Study of Stimulant Drug Treatment for ADHD and Academic Progress in Children

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Background: Evidence is sparse regarding long-term effects of stimulant treatment on academic progress among children with attention-deficit/hyperactivity disorder (ADHD).

Objectives: We evaluated the hypothesis that later start of stimulant treatment for ADHD adversely affects academic progress in mathematics and language arts among 9-to 12-year old children.

Methods: We linked nationwide data from the Icelandic Medicines Registry and the Database of National Scholastic Examinations. The study population comprised 11,872 children born 1994–1996 who took standardized tests in both 4th and 7th grade. We estimated the probability of academic decline (drop of ≥5.0 percentile points) according to drug exposure and timing of treatment start between examinations. To limit confounding by indication we concentrated on children who started treatment either early or later, but at some point between 4th grade and 7th grade standardized tests.

Results: In contrast with non-medicated children, children starting stimulant treatment between their 4th and 7th grade tests were more likely to decline in test performance. The crude probability of academic decline was 72.9% in mathematics and 42.9% in language arts for children with a treatment start 25–36 months after the 4th grade test. Compared with those starting treatment earlier (≤12 months after tests), the multivariable adjusted risk ratio (RR) for decline was 1.7 (95% confidence interval [CI] 1.2–2.4) in mathematics and 1.1 (95% CI 0.7–1.8) in language arts. The adjusted risk ratio of mathematics

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decline with later treatment was higher among girls (RR, 2.7; 95% CI 1.2–6.0), than boys (RR, 1.4; 95% CI 0.9–2.0).

Conclusions: Later start of stimulant drug treatment for ADHD is associated with academic decline in mathematics.

290. Trends in Antidepressant Prescribing in Children in the United Kingdom, a Study in The Health Improvement Network (THIN)

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Background: Doubts have been raised over the benefits and safety of the use of selective serotonin reuptake inhibitors (SSRIs) in children. In December 2003, the UK Committee on Safety of Medicines (CSM) advised against initiation of treatment with SSRIs in children other than fluoxetine.

Objectives: We aimed to determine trends in the incidence of antidepressant prescriptions for children issued by general practitioners (GPs) following this contra-indication.

Methods: We identified 1,502,753 children ≤18 years who were registered with their GP for ≥1 year in The Health Improvement Network (THIN) UK primary care database. Trends in incidence of antidepressant prescribing were examined between 1995 and 2010 using interrupted time-series analysis.

Results: Overall, 25,473 (2%) children had been prescribed antidepressants and SSRIs were prescribed to 16,925 (1%) children. SSRI prescription rates decreased from 3.2 (95% CI: 3.0–3.3) per 1,000 PYAR in 2002 to 1.7 (95% CI: 1.7–1.8) per 1,000 PYAR in 2005. However, since then they have risen to 2.7 (95% CI: 2.6–2.8) per 1,000 PYAR in 2009. Prescription rates for contra-indicated SSRIs dropped after 2002, in particular for paroxetine. On the other hand, rates for non-contra-indicated fluoxetine did not change, though rates did show a small dip around 2004. After 2005, prescription rates for individual SSRIs slightly increased again, with the exception of citalopram which saw a sharp increase and paroxetine which was prescribed only sporadically after this time. For tricyclic antidepressants, there was a steady decline over the entire study period. However, there was a small increase in prescription rates of amitriptyline between 2006 and 2009.

Conclusions: Rates of SSRI prescriptions showed a significant drop around the time of the CSM advice. This could indicate caution on the part of GPs in prescribing antidepressants to children. However, after 2005 rates for all SSRIs, except paroxetine, were increasing again. This is in line with results from observational studies that found no increased risk of suicidal behaviour with SSRIs.

291. Trends in Paediatric ADHD Drug Prescription in the UK and Cardiovascular Event Rates

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Background: The use of ADHD (attention deficit and hyperactivity disorder) drugs in children has steadily increased during the past decades in Europe and in the USA. Concurrently, concerns were raised about potential adverse reactions of these drugs. In 2008, NICE published a new guideline regarding the management of ADHD in the UK emphasizing that drug treatment should only be given as first line treatment to children with severe ADHD impairments.

Objectives: To investigate the prescription of ADHD medications and measure cardiovascular event rates in children in the UK.

Methods: We included all patients under 16 registered in the General Practice Research Database who received at least one prescription of any ADHD drug between 1992 and 2010. Trends in prevalence and incidence of ADHD drugs use in children were calculated between 1995 and 2010. Background rates of cardiovascular events in methylphenidate users were determined and compared with non users.

Results: The overall prevalence of ADHD drug use in children under 16 increased 34-fold between 1995 and 2008 from 1.4 to 48.4 per 10,000 children in the UK followed by a slight decrease to 46.3 per 10,000 children in 2010. Incidence of new users of the drugs follow the same pattern decreasing from 10.1 to 8.9 per 10,000 children between 2007 and 2010. We identified that 56.2% (95% CI: 54.6–57.9) of children were still under treatment after 6 years. We observed no serious cardiovascular events or Q-T prolongations recorded in children using methylphenidate and a very low number of arrhythmias.

Conclusions: Following recent guidelines and the fear of an increased cardiovascular risk in children taking ADHD drugs, their use in children in the UK seemed to reach a "plateau." Although ADHD treatment duration is longer in the UK than in the US, our analysis confirms the findings of large US studies showing very low rates of cardiovascular events in children taking methylphenidate.

292. Antipsyhotic Use by U.S. Medicaid Insured Youth: Impact of Eligibility and Psychiatric Diagnosis

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Background: The increased use of antipsychotic (ATP) medication for US youth over the last 2 decades has been profound. No previous study has detailed the impact of Medicaid eligibility categories and diagnosis on this increased use.

Objectives: To broadly characterize temporal trends across a decade in the use of ATP medication by Medicaid-insured youth with respect to their Medicaid-eligibility status and clinical-reported psychiatric diagnosis.

Methods: This cross-sectional study analyzed computerized claims data on continously enrolled Medicaid-insured youth aged 2–17 years from a mid-Atlantic U.S. state comparing patterns in 2006 with 1997. Bivariate analyses and a multivariable logistic regression model were employed to quantify temporal changes in antipsychotic use primarily in relation to these youths' major Medicaid eligibility categories (TANF [very low family income], s-CHIP [low familiy income], SSI [disability], and foster care) and to their clinician-reported psychiatric diagnoses. A second multivariable logistic regression modelling was employed to examine temporal changes in demographic and clinical features among the subgroup of ATP users with a psychiatric diagnosis.

Results: The prevalence of ATP use increased from 1.2% in 1997 to 3.2% in 2006. Youth enrolled in s-CHIP had a greater increase in adjusted-odds (AOR 5.9 [4.5, 7.7]) of ATP use in 2006 than in 1997 compared to youth in the other eligibility categories (TANF AOR 3.6 [3.2, 4.0]; Foster Care 4.1 [3.7, 4.6]; SSI 2.8 [2.6, 3.1]). Among ATP users with a psychiatric diagnosis, youth with externalizing behavior disorders had greater proportional increases across the decade than youth diagnosed with schizophrenia, other psychoses, and pervasive developmental disorders. This proportional increase was also significant for African American and Hispanic youth compared with white youth.

Conclusions: The expansion of antipsychotic medication use from 1997 to 2006 was most prominent among youth who qualified for Medicaid because of low (s-CHIP) family-income and reflects increased medication use for behavioral problems.

293. Psychotropic Treatment among Youth in Foster Care in the U.S.

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Background: High rates of psychotropic medication use in foster care youth, particularly for antipsychotics, have been a subject of concern in the U.S.

Objectives: To provide a better understanding of high psychotropic medication use among the foster care population.

Methods: We used Medicaid data from 43 states to examine patterns and predictors of antipsychotic (AP) and other psychotropic use among youth in foster care in the U.S. aged 6–17 in 2001 and 2005. Services and diagnoses received during the year were examined using a hierarchical diagnostic classification, with comparisons to the general population of youths. We examined trends in antipsychotic use over this time period and the contribution to these trends of evolving diagnostic patterns and changing treatment rates within diagnostic categories.

Results: In 2005, 13.6% of foster youth (vs. 3.4% of non-foster youth) received APs, a 46% increase from 2001. The higher rate among foster youth reflects in part, but not fully, differing rates of psychiatric diagnoses. fifty-four percent of foster youths and 22% of all youth had received a psychiatric diagnosis in 2005. 4.6% of foster youth vs. 1.0% of all youth were diagnosed with bipolar disorder; 23.5% vs. 9.2% with ADHD; and 13.1% vs. 3.5% with conduct or disruptive behavior disorder. Seventy-four percent of AP-treated foster youth had not been diagnosed with conditions for which an FDA antipsychotic indication for youth exists. Most also received other psychotropic medications including stimulants, antidepressants and mood stabilizers. Many AP-treated youth appeared to receive few or no specialty mental health services. Geographical variation in AP treatment was dramatic, with rates varying from 5% to more than 20% among states.

Conclusions: Rates of antipsychotic treatment were much higher among foster than non-foster youth. AP use among foster youth was more likely to be associated with bipolar diagnoses and less likely to be associated with ADHD diagnoses than in the general youth population, although ADHD remained strongly associated with AP treatment in both populations. Most use was off-label. Results suggest the need for more systematic review and evaluation of AP use in this population.

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294. Psychotropic Drug Utilization in Children with Concomitant ADHD and Anxiety

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Background: Children with concurrent ADHD and anxiety might be less responsive to stimulants and more sensitive to side effects. Other psychotropic drugs use in this population deserves investigation.

Objectives: To determine the prevalence of psychotropic drug use in children with concurrent ADHD and anxiety.

Methods: This is a cross-sectional drug utilization study in 28 US states Medicaid fee-for-service programs from 1999 to 2006. Patients aged 18 and below with at least one continuous 90-day period of concurrent ADHD and anxiety diagnoses were enrolled. ADHD was defined to persist from first outpatient claim to the last with an extension of 1 year. Anxiety was defined to persist for 6 months from first and any subsequent claim. Periods with diagnoses of ODD/CD, depression, bipolar disorder, Tics/Tourette syndrome or schizophrenia were excluded. One hundrend and two psychotropic drugs including ADHD drugs, antidepressants, antipsychotics, anticonvulsants, anxiolytics, lithium and α-agonists formed the drug pool. The duration of prescription fills was defined as the days' supply plus 10 days to avoid breaks due to late refill. The percentage of person-days with specific drug or drug-drug combinations (based on ≥1 day or 90-days of overlap) in ADHD-anxiety periods was calculated.

Results: We identified 52,637 patients with 17,676,551 ADHD-anxiety person-days, in which 29.8% were free of treatment, 42.0% with monotherapy, 20.8% with dual therapy, and 7.5% with >2 therapies. Top monotherapy regimens included methylphenidate (13.2%), amphetamine (10.4%), atomoxetine (2.7%), risperidone (2.7%), clonidine (1.5%) and sertraline (1.3%). Methylphenidate plus clonidine or risperidone were the most common drug-drug combinations (1.1% and 1.3%). The percentages dropped to 0.3% and 0.4% with 90-day minimum overlap requirement.

Conclusions: ADHD medications play a key role in the treatment of children with ADHD and anxiety despite possible lower response rate and higher adverse events rate. Antidepressants and atypical antipsychotics, specifically sertraline and risperidone, were the most common non-ADHD therapies in US practice.

295. Prevalence and Determinants of Psychotropic Drug Use in Institutionalized Children and Adolescents with Mild Intellectual Disability and Behavioural Problems

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Background: In spite of limited evidence of effectiveness, and safety concerns it is common practice to prescribe psychotropic drugs for psychiatric and behavioral problems to children and adolescents with intellectual disability (ID). Studies on the prevalence and determinants of psychotropic drug use have mainly been performed in adults with ID or children without ID.

Objectives: The aim of this study is to assess the frequency and type of psychotropic drug use by children and adolescents with mild intellectual disability (MID) and behavioral problems and determinants thereof.

Methods: In 2011 a cross sectional study was performed in children and adolescents with MID and behavioral problems institutionalized in eight inpatient treatment facilities in the Netherlands. Demographic data, psychiatric diagnoses, nature of the behavioral problems, level of intellectual functioning and medication data were extracted from the medical records using a standardized data collection form. Relative risks (RR) and adjusted relative risks (ARR) for the association between patient characteristics and psychotropic drug use were estimated with Cox regression analysis.

Results: Data of 472 patients were collected. Of 139 (29.4%) patients used any psychotropic drug of which 72 (15.3%) used antipsychotics (mainly risperidone) and 70 (14.8%) used psychostimulants. Boys had a 2.0 (1.4–2.8 95% CI) higher relative risk of using psychotropic drugs compared to girls. Behavioral problems were associated with psychotropic drug use with an ARR of 2.1 (1.3–3.3 95% CI), adjusted for gender and age). Verbal aggression, physical aggression, restless hyperactive – and self-injurious behavior were significantly associated with antipsychotic use.

Conclusions: In a large representative sample of institutionalized children and adolescents with MID and behavioral problems 29.4% used at least one psychotropic drug. This high prevalence is worrying because of the lack of evidence of effectiveness and the potential of adverse effects.

296. Continuity and Adherence with Stimulant Therapy in Children and Adolescents in Germany: A Claims Data Analysis

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Background: The prescribing volume for stimulants is still increasing in Germany. However, little is known about patterns of use.

Objectives: The aims of the study were to assess continuity and adherence of stimulant use during the first 2 years of treatment in 3 cohorts of incident users between 2000/2001 and 2005/2006 and to compare adherence rates between these cohorts.

Methods: Data base: claims data of a large statutory health insurance fund (AOK, federal state of Hesse). Insured children/adolescents between 4 and 17 years of age: cohort 1 (C1: 2000/2001): N = 37,966, cohort 2 (C2: 2002/2003): N = 37,299, cohort 3 (C3: 2004/2005): N = 35,380. Mean age in years C1: 10.6, C2: 10.8, C3: 10.9. Study population: insured with incident prescribing of methlyphenidate/atomoxetine, i.e., no stimulant medication 2 years before the first prescription in the respective year of observation. Incident users: C1: n = 259, C2: n = 249, C3: n = 228. Follow-up: 8 quarters a 90 days each. For an 80% adherence, a prescribing volume of 150 DDD stimulants per year was necessary when supposing a treatment with 1 DDD/day and no treatment during weekends and holidays. To rule out patients with treatment attempts, adherence was assessed for those with at least 2 prescriptions.

Results: The percentage of those with 80% adherence in the first year of treatment increased: C1: 39%, C2: 44%, C3: 54%. Correspondingly, the percentage of patients with <150 DDD of stimulants declined: C1: 61%, C2: 56%, C3: 46%. The percentage of high users with more than 365 DDD increased since 2000: 2% (C1), 8% (C2, C3). Discontinuation after the first quarter of incident use was observed in 24% of the users in C1 compared to 22% (C2) and 21% (C3). Continuous therapy with at least one prescription in every quarter during the first eight quarters rose from 21% (C1) to 23% (C2) and 29% (C3).

Conclusions: The utilisation pattern changed since 2000 resulting in longer treatments and a higher percentage of adherent stimulant users. Whether an indication for treatment was given or improvement achieved, can not be analysed with this study type. However, changes in every day treatment habits can be well assessed using claims data.

297. Attention Deficit/Hyperactivity Disorder: Prescribing Patterns of Methylphenidate and Atomoxetine

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Background: Drugs for Attention Deficit/Hyperactivity Disorder are often said to be over-prescribed and overused in South Africa, although evidence for this is still lacking.

Objectives: To determine the prescribing of psychostimulant drugs to patients with Attention Deficit/Hyperactivity Disorder in a South African private sector patient population, focusing on methylphenidate and atomoxetine.

Methods: A retrospective, cross-sectional drug utilization study was conducted on prescription data of a national community pharmacy group in South Africa for 2010. All records for patients 18 years and younger who received one or more prescriptions for methylphenidate and/or atomoxetine (ATC Code N06BA) during the year were analysed.

Results: A total of 15,681 children received 45,603 prescriptions for methylphenidate and/or atomoxetine at an average cost of R387.75 per prescription. The average age of patients was 11.87 (SD = 3.04) years. Nearly three-quarters of patients (71.84%) were males. Similar to previous South African studies, most prescriptions were for methylphenidate (90.00%), followed by atomoxetine (10.00%). Approximately two-thirds of prescriptions were tablet formulations (62.65%). There are no generic equivalents available for atomoxetine on the South African market. Nearly half of all prescriptions (47.39%) were dispensed to children aged 6–11 years. Although these products are not recommended for children under 6 years, 197 prescriptions were dispensed to 113 patients younger than 6 years. Clear peaks and troughs in the number of prescriptions could be observed during certain months of the year, indicating that drug holidays were used. Prescribing peaked in May and November (traditional examination months), while troughs were observed in June and December (school holiday months). The average Prescribed Daily Dose (PDD) for methylphenidate was 26.27 (SD = 15.27) mg (DDD = 30 mg) and for atomoxetine 38.70 (SD = 21.45) mg (DDD = 80 mg). Most prescriptions were dispensed in the Western Cape and Gauteng provinces.

Conclusions: Overprescribing could not be proved in this study. The lower dosages prescribed and drug holiday utilisation warrants further qualitative investigation.

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299. Iatrogenic Aluminum and Neurocognitive Performances of Moroccan Children

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Background: Aluminum is a neurotoxic present in numerous sources such as air, food, household materials, water, cosmetics and drugs. Once entirely absorbed in gastrointestinal tract, it could impair neurocognitive performances.

Objectives: The evaluation of the general intelligence and working memory in the urban, periurban and rural schooled children (aged 6–8 years) living in the Gharb plain (North-West of Morocco) and the study of the possible relationship between the neurocognitive performances and the consumption of iatrogenic aluminum.

Methods: This cross-sectional study is conducted among 129 school-aged children living in the urban, periurban and rural region of the Gharb plain (N-W of Morocco). The children suffering from cranial traumatism or neurologic disease are excluded. Neurobehavioral performances are measured by Raven's Standard Progressive Matrices (RSPM) and Memory Sub-test of WISC III (Wechsler Intelligence Scale for Children). The consumption of iatrogenic aluminum and the quality of children's lives are evaluated by the questionnaire. Statistical analyses are realized by ANOVA 1, LSD and Pearson correlation coefficient.

Results: The obtained results show that the best scores of RSPM are registered among the urban children ($p < 0.01$) and the high rate of working memory impairments (66.67%) is registered among rural children. Significant correlations between performance in RSPM ($p < 0.05$), working memory ($p < 0.05$) and consumption of iatrogenic aluminum is also found.

Conclusions: The children's intelligence and working memory appear in connection with iatrogenic aluminum consumption; however, several factors (environmental, psychological, socio-economical, and nutritional factors) could influence these performances. So, a deeper investigation is needed for studying all these factors.

300. Methadone and Perinatal Outcomes – A Prospective Cohort Study

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Background: Methadone use in pregnancy has been associated with adverse perinatal outcomes and neonatal abstinence syndrome (NAS). The determinants of the incidence of NAS are poorly understood.

Objectives: This study aimed to examine perinatal outcomes and NAS in relation to (1) concomitant drug use and (2) maternal methadone dose at delivery.

Methods: A prospective cohort study was carried out in two tertiary care maternity hospitals. Pregnant women on methadone maintenance treatment were recruited from specialised antenatal clinics. Enzyme immunoassay was used for urinalysis to detect evidence of concomitant use of opiates (excluding methadone), benzodiazepines, or cocaine in maternal and neonatal samples. Perinatal outcomes included preterm birth (< 37 weeks' gestation), small for gestational age (< 10th centile) and neonatal unit admission. Outcomes related to NAS included the incidence of medically treated NAS, peak Finnegan score, cumulative dose of NAS treatment and duration of hospitalisation.

Results: Of 117 women participated in the study. Of the 114 liveborn infants 11 (9.6%) were born preterm, 49 (42.9%) were small for gestational age, 56 (49.1%) had a neonatal unit admission and 29 (25.4%) were medically treated for NAS. Neonates exposed to methadone only had a shorter duration of hospitalisation than those exposed to methadone and concomitant drugs (median 5.0 days [IQR 5.0–7.0] vs. 6.0 days [IQR 5.0–22.5], $p = 0.03$). Neonates exposed to methadone doses ≥80 mg required higher cumulative doses of morphine treatment for NAS (median 13.2 mg [IQR 10.5–19.9] vs. 19.3 mg [IQR 16.1–34.4], $p = 0.03$). The incidence and duration of NAS did not differ between the high and low dose groups.

Conclusions: Adverse perinatal outcomes appear to be common among methadone-maintained women. Concomitant exposure to opiates, benzodiazepines or cocaine was associated with a longer duration of neonatal hospitalisation. The incidence and duration of NAS were not affected by maternal methadone dose, though the severity of NAS, as indicated by the amount of morphine required for treatment, appeared to be increased with higher methadone doses.

301. Psychomotor Effects of In Utero Exposure to Psychotropic Medications: A Comparative Study in EFEMERIS Database

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Background: Little is known about neurodevelopment of children exposed to psychotropic drugs during pregnancy.

Objectives: The objective of the present study was to compare psychomotor development between children exposed in utero to psychotropic medications and children unexposed to these drugs in utero.

Methods: We performed a case-control study in EFEMERIS, a French prescription database including 40,355 pregnant women. EFEMERIS is a database including prescribed and delivered drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnostic Centre). We compared neurodevelopment at 9 months and 2 years between children exposed to psychotropic medications (anxiolytics, antidepressants, neuroleptics and antiepileptics) during the second and/or third trimesters of pregnancy and children unexposed to these drugs in utero.

Results: Of 493 (1.5%) newborns exposed during the second and/or the third trimesters of pregnancy to psychotropic drugs were compared to 32, 303 controls. Of 298 (0.9%) infants were exposed to anxiolytics, 207 (0.6%) to antidepressants, 83 (0.3%) to antiepileptics and 81 (0.3%) to neuroleptics. Prematurity rate was similar in the 2 groups. Exposed infants have more motor difficulties at 9 months (8.8% vs. 6.1%; $p = 0.01$) and 2 years (1.8% vs. 0.4%; $p = 0.003$) than controls and more negative items about mental development at 2 years (2.2% vs. 1.0%; $p = 0.04$). After adjustment on mother age, prematurity and malformations, the relative risk of abnormal motor development increased (RR = 1.6 [1.1–2.2] at 9 months and RR = 4.8 [2.1–11.0] at 2 years]). More abnormal psychomotor development was observed in children exposed to antiepileptics (mainly sodium valproate), neuroleptics or antidepressants in particular.

Conclusions: The present study found an association between psychotropic drug prescription during second and third trimesters of pregnancy and abnormal psychomotor development. However, these results must be discussed according to other confounding factors, like mothers diseases, social environment.

302. Infant and Childhood Neurodevelopmental Outcomes Following Prenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs)

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Background: Experimental and observational studies have suggested an increased risk for adverse neurodevelopmental outcome after prenatal exposure to SSRIs.

Objectives: To describe the methods of an ongoing population-based study examining the association between prenatal SSRI exposure and neurodevelopment until age 15.

Methods: This is a cohort study based on national registers in Finland: the Medical Birth Register, the Register of Congenital Malformations, the Hospital Discharge Register, the Drug Reimbursement Register, and the Population Register. The total study population includes 845,345 women and their live-born, singleton offspring born during January 1st 1996–December 31st 2010. The prevalence of psychiatric and neurodevelopmental outcomes in offspring exposed prenatally to SSRIs is compared to offspring exposed to prenatal depression and unexposed to SSRIs. Logistic regression is used to assess the association between exposure and outcome, and specific models to account for correlated outcomes within families and differences in duration of follow-up.

Results: The use of SSRIs within the pregnant population increased from 0.4% in 1996 to 3.4% in 2008 (data not yet obtainable until 2010). The prevalence of maternal depression and depression-related psychiatric diagnoses within 1 year before and until the end of pregnancy was 1.7% (years 1996–2010). The cumulative incidence of any registered psychiatric or neurodevelopmental disorder in the offspring population born during 1996–2010 was 6.9% in 2010 (age range 0–14 years).

Conclusions: The study carries significant public health importance in providing information on prenatal exposure to SSRIs and long-term neurodevelopment. This study is a component of an international, collaborative research

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project together with the Conte Center, NY, with several linked projects including experimental animal models and clinical neurobiological studies on infant outcomes following SSRI exposure *in utero*, generating a comprehensive bidirectional model for current translational epidemiology. The study is funded by a NIH Grant P50MH090966 and the Sackler Center.

303. The Association between ADHD Treatment in Childhood and Substance Use and Abuse in Adults – A Long-Term Follow-Up

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Background: Children, adolescents and adults with ADHD are known to be at risk for substance use and abuse. A relation between stimulant treatment and the risk for substance use and abuse has been suggested.

Objectives: To describe the association between stimulant treatment and drug use and abuse at followup in adults diagnosed with ADHD in childhood or adolescence.

Methods: A cohort study designed to evaluate global and clinical outcomes in adulthood of subjects who received psychiatric care during their childhood or adolescence between January 1984 and December 2004 (T1). Subjects were traced from September 2006 until February 2010 (T2). Subjects meeting all of the following criteria were included for follow-up: an ADHD diagnosis based on DSM criteria at T1, aged 18 years or younger at T1, aged 18 years or older at T2. Mean followup was 14.6 years with a mean age at T2 of 28.7. Associations between parameters of behavioural symptoms and treatment in childhood or adolescence and follow-up measures, collected by questionnaire, concerning medication use and drug use (ever used) and abuse (daily used) were investigated.

Results: Nearly 30% (N = 398) of the 1,349 subjects returned the questionnaire at T2. Fifty percent of the responders (199 subjects) reported that they ever used drugs like cannabis, party drugs and/or hard drugs. Risk for drug use in general (HR 2.0 [95% CI 1.2–3.3]) and cannabis use HR 1.6 [95% CI 1.1–2.2]) was increased in those with a history of stimulant treatment ever, adjusted for potential confounders including psychiatric comorbidity. Adults, who were at T1 not only diagnosed with ADHD but also with ODD or CD had a higher risk for drug use in general (HR 1.8 [95% CI 1.0–3.1]) and for cannabis use (HR 1.7 [95% CI 1.2–2.5]) and abuse (HR 2.0, [95% CI 1.2–3.3]).

Conclusions: A history of stimulant treatment ever in life increased the risk for drug use in all categories: cannabis, party- and hard drugs in adults diagnosed as a youngster with ADHD. It is discussed whether stimulant treatment may predict especially experimental cannabis use and might even be protective for addiction.

304. Parent's Use of Hypnotics Predicts Alimemazine Use in Infants and Toddlers

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Background: The antihistamine alimemazine is frequently used among infants and toddlers in Norway to alleviate sleeping problems in spite that the effect and safety of this practice has been disputed.

Objectives: To study the association between the parent's hypnotic use 1 year prior to pregnancy and the use of alimemazine in children 0–3 years of age.

Methods: An observational longitudinal study using data from two nationwide; the Norwegian Prescription Database and the Norwegian Medical Birth Registry.

Setting: All children born in Norway in 2006 were eligible. Only the first child born this year of every mother and/or father was included (N = 56,511).

Exposures: Prescriptions of benzodiazepine hypnotics and z- hypnotics (ATC-code N05CD and N05CF) filled by the mother or the father or both in the 1 year period prior to pregnancy.

Main outcome measures: Prescriptions for alimemazine (ATC-code R06AD01) to children 0–3 years of age.

Statistical analysis: Logistic regression.

We adjusted for the prescriptions of antidepressants to the mother, infant's gender, gestational age, prescriptions for antibiotics, respiratory agents and dermatological steroids, parent's age, number of children and regions of the country.

Results: Of 1,578 children (2.8%) received a prescription for alimemazine. Use of hypnotics both among fathers (adjusted odds ratio 1.7; 95% CI 1.2–2.3), mothers (1.8; 1.4–2.3) or both (2.9; 1.5–5.4) increased the risk of the child receiving alimemazine. The mother's use of antidepressants, infant male gender, being born preterm, having received prescriptions for antibiotics, dermatological steroids or for drugs for obstructive respiratory diseases all increased the chance of receiving alimemazine.

Conclusions: Use of hypnotics by the parents increased the risk of an alimemazine prescription for the child. The association with parent hypnotic use may indicate that sleep problems themselves or the tolerance for insomnia may to some degree be inherited.

305. Pediatric Use of Single-Entity Extended Release Oxycodone

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Background: Medications are increasingly prescribed to pediatric patients however less is known about drug safety and efficacy in this population. While single-entity extended release oxycodone (ER oxycodone) is not indicated for children, data suggest that it is used in this population.

Objectives: Describe demographic/ clinical characteristics of pediatric patients who receive prescriptions for ER oxycodone.

Methods: Identified patients ≤16 years of age with ≥1 incident prescription for ER oxycodone in the Henry Ford Health System (HFHS) or the HealthCore Integrated Research Database (HIRD^{SM}), from 1/2000 to 9/2011 (HFHS) or 1/2001 to 9/2011 (HIRD). Limited cohort to pts with 12 months of prior continuous eligibility (except for those < 1 year of age). At the HFHS reviewed electronic medical records to verify prescription, determine indication, and post-surgery initiation time. Used descriptive statistics to calculate demographic (HFHS and HIRD) and clinical characteristics (HFHS). Ongoing claims-only descriptive analyses are in progress using the HIRD.

Results: Preliminary results show 597 patients were exposed to ER oxycodone; 319 (53%) were male and 509 (85%) were of 12–16 years old. In the HFHS: top indications were for orthopedic conditions (23%) and indications in the Other category (73%); ER oxycodone was started within 71 hours after surgery in 46% of patients; the mean duration of use was 10.2 days (standard deviation 6.5); and 73% were prescribed > 80 mg/day. Further, the top concomitant medication classes were analgesics (64%), medications in the Other category (45%), and laxatives (32%). Top comorbidities were: comorbidities in the Other category (59%), pain-related comorbidities (36%), and respiratory (27%). In pilot HFHS safety data, adverse events (AE) included: headache (14%), constipation (9%), and nausea/vomiting (9%).

Conclusions: The largest proportion of pediatric patients prescribed ER oxycodone are older adolescent males. In the HFHS population, the drug was prescribed for orthopedic conditions, pain control, and in combination with other analgesics. AEs experienced were headache, constipation, and nausea/vomiting. Ongoing analyses, including safety data, in the HIRD are underway.

306. Use of Single-Entity Oxycodone and Oxycodone Combination Products in Pediatric Patients

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Background: Few opioid drugs are indicated for pediatric patients however opioids, including oxycodone, are sometimes used to treat pediatric pain. The circumstances in which pediatric patients receive these drugs have not been fully explored.

Objectives: To describe the characteristics of pediatric patients (≤16 years of age) prescribed oxycodone products, as single-entity extended release (ER) formulations or other oxycodone products, for the treatment of pain.

Methods: This study was a descriptive analysis of characteristics of pediatric patients prescribed oxycodone either as ER single-entity drug or as another oxycodone product. The study used electronic medical record data from the US-based Henry Ford Health System for 2000–2010.

Results: A total of 151 patients prescribed oxycodone-containing products between 2000 and 2010 were identified. Of these 26 (17%) patients were prescribed single-entity ER oxycodone. Most patients prescribed oxycodone were older adolescents; 68% of ER oxycodone users and 87% of the other oxycodone product users were age 14–16. Those prescribed ER oxycodone were predominantly male (71%), while those prescribed other oxycodone products were 52% male. Indications for use varied by treatment; for those prescribed ER oxycodone, 39% received it for orthopedic pain/injuries, 21% for post-surgical pain, and 18% for pain associated with cancer. Those taking other products had similar indications but also a great deal of short-term use for dental or other pain conditions (60%). Patients prescribed other oxycodone products were more likely to be exposed for short duration compared to those who received ER oxycodone; 88% of patients received other oxycodone products for < 7 days, while for single-entity ER, 50% received it for < 7 days, 25% for 7–10, and 25% for > 10. Many of the patients taking ER oxycodone (36%) transitioned to another opioid or a combination of opioids and NSAIDS after initial treatment.

Conclusions: Pediatric patients who receive oxycodone tend to be older adolescents. Indication for use and duration of use vary, with shorter use reported for immediate-

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release single-entity or combination products compared with single entity ER products.

307. Pediatric Insomnia and Utilization of Prescription Sedative-Hypnotics: A Descriptive Study

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Background: Use of sedative-hypnotic drugs in pediatric patients is increasingly common but the characteristics of these patients, including their diagnoses, have not been well-characterized.

Objectives: To describe the characteristics of pediatric patients (≤16 years of age) prescribed sedative-hypnotic drugs and to contrast those with vs. without a medical claim for insomnia.

Methods: This study was a descriptive cohort analysis of characteristics of pediatric patients who used prescription sedative-hypnotics. The study was conducted in the US-based Marketscan commercial healthcare claims database for 2008–2010. Patients included those with and without ICD-9 codes for insomnia who were treated with sedative-hypnotics including zolpidem, zaleplon, eszopiclone, short-acting benzodiazepines (alprazolam, lorazepam) or a long-acting benzodiazepine, diazepam. Patient characteristics included demographics and selected comorbidities. Statistics were primarily descriptive; RRs with 95% confidence intervals were calculated for key comparisons.

Results: There were 35,570 pediatric patients who were prescribed sedative-hypnotics, 40,104 with a claim for insomnia and 1,819 (5%) with both insomnia and a sedative-hypnotic prescription. The latter varied by drug, from 2% for short-acting benzodiazepines to 29% for eszopiclone. Diazepam was the most commonly used sedative-hypnotic (used in 61%), followed by short-acting benzodiazepines (34%) and zolpidem (8%). Most (92–93%) children treated with zolpidem, zaleplon, and eszopiclone were age 12–16, while benzodiazepines were used more often in patients under 12. A claim for insomnia along with ADHD was found in only 0.1–2.4% of children prescribed these drugs. Children without an insomnia diagnosis who received sedative-hypnotics were primarily adolescents (57% age 12–16), while those diagnosed with insomnia who received these drugs were more diverse in age.

Conclusions: Only a small proportion of pediatric patients who are prescribed sedative-hypnotic drugs also have a claim for insomnia; this varies by drug. For sedative-hypnotics such as zolpidem, most use is in older children, while benzodiazepines are used more often in younger children.

308. Analysis of Cardiovascular Events or Diabetes Mellitus during Androgen Deprivation Therapy in Korean Prostate Cancer Patients

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Background: ADT (Androgen Deprivation Therapy) is widely used as prostate cancer treatment. Recently, adverse effects of ADT have been issued about increasing risk of cardiovascular disease (CVD) and diabetes mellitus (DM).

Objectives: The purpose of study is to investigate this association between ADT and CVD or DM.

Methods: The study included 526 patients treated with ADT and 262 patients treated with radical retropugic prostatectomy (RRP) at the National Cancer Center in Korea from January 2001 through December 2008. Study subjects were those who have node-negative localized and advanced localized prostate cancer. After excluding patients with a history of radiation therapy, node-positivity, evidence of metastasis and pre-existing CVD and DM, 96 patients treated with ADT and 90 patients with RRP were remained for the analysis. The data, followed-up until December 2010, were retrospectively reviewed from electronic medical records (EMR). To test the difference in the incidences of CVD or DM between RPP and ADT groups, exact logistic regression analysis was performed. Baseline variables including age, body mass index, family history of CDV or DM, history of smoking and T-stage were examined to check the imbalance between two groups. Variables that were significantly imbalanced between groups were considered in the multivariable logistic regression.

Results: Newly developed CVD or DM were found in 7 out of 96 patients in the ADT group, and 1 out of 90 patients in the RRP group. The incidence of CVD or DM was higher in ADT group than RRP group, but it failed to reach statistical significant at 0.05 with the observed p-value = 0.066. Subgroup analysis based on different treatment drugs (LHRH agonists + antiandrogen [AA], or each alone) revealed that the incidence of CVD or DM was higher in the combination of LHRH agonists and AA group (odds ratio = 2.05; 95% CI 1.01–4.12; p = 0.043). However, it was not significant in LHRH agonists alone, and AA alone groups.

Conclusions: Our study found that there is a tendency of increased CVD or DM in Korean men with prostate cancer treated with ADT compared to RRP, however, it failed to reach statistical significance.

309. Adverse Events to Antiretroviral Therapy for HIV-Infected Children in Lagos, Nigeria: A Retrospective Study

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Background: An effective HAART program would require adequate monitoring of adverse events associated with the ARV drugs.

Objectives: To investigate the pattern of ARV drug combinations prescribed for HIV- infected children and also to document their suspected adverse events.

Methods: Retrospectively, we reviewed the case files of 80 HIV-infected children at the APIN clinic, Lagos University Teaching Hospital (LUTH) in Nigeria. Patients were included if <15 years old, had used ARV drugs for at least a year, and had not progressed to full blown AIDS. Information about the demography, mode of contracting HIV, presenting symptoms, co-morbid diseases and intercurrent infections, co-administered drugs, the ARV drug regimen prescribed, and their clinical and laboratory suspected adverse events were extracted. Statistical analysis was with Statistical Package for the Social Sciences (SPSS), version 16. Comparisons between the baseline and follow up data were made using the student t-test at a significance level of $p < 0.05$.

Results: The median age of the patients was 3 (IQR: 1.1–6.0) years. They were predominantly female (46; 57.5%). Zidovudine- lamivudine- nevirapine combination (74; 92.5%) was the most frequently prescribed first-line regimen. Of the 33 patients who changed their first-line regimen, abacavir-lamivudine-rotinavir boosted with lopinavir (11; 33.3%), and zidovudine- lamivudine- abacavir- rotinavir boosted with lopinavir (8; 24.2%) combinations were the second-line regimens frequently prescribed. Nevirapine-induced skin rashes (18; 22.5%), and zidovudine-induced pallor (5; 6.3%), vomiting (5; 6.3%) and abdominal pains (2; 2.5%) were the commonest clinical adverse events observed. Macrocytosis 22/72 (20.6%), anaemia 6/72 (8.3%), and thrombocytopenia 2/72 (2.8%) were the commonest haematological adverse events associated with zidovudine.

Conclusions: ARV regimen used at the APIN clinic, LUTH has a good safety profile. The few adverse events observed in this study suggest a need for prospective pharmacovigilance to effectively monitor the toxicities of ARV drugs.

310. Relative Age, Academic Performance and Stimulant Prescribing for ADHD: A Nationwide Cohort Study

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Background: The impact of relative age at school entry on later academic progress and risk of attention-deficit/hyperactivity disorder (ADHD) remains controversial.

Objectives: To evaluate whether being among the youngest in the school year is associated with poorer academic performance into adolescence and increased risk of being prescribed stimulant drugs for ADHD.

Methods:

Design: A nationwide population-based cohort study linking data from national registries of prescription drugs and standardized scholastic examinations.

Setting: Iceland 2003–2009.

Participants: All children born in 1994–1996 who took standardized tests in Iceland at age 9 and age 12 at the age assigned grade level, in total 11,785.

Main outcome measure: Risks of receiving low test scores (0–10th percentile) and being prescribed stimulants for ADHD. Comparisons were made according to children's relative age in the school year.

Results: Mean test scores in mathematics and language arts were lowest among the youngest children within the school year at age 9 and age 12, although the gap attenuated. Compared with children in the oldest third of the school year, those in the youngest third had an increased relative risk of receiving a low test score at age 9 for mathematics (1.9; 95% confidence interval (CI) 1.6–2.2) and language arts (1.8; 95% CI 1.6–2.1), while at age 12 the relative risk was 1.6 in both subject areas. Children in the youngest third of the school year were 50% more likely (1.5; 95% CI 1.3–1.8) than those in the oldest third to be prescribed stimulants between ages 7 and 14. The relative age effect on academic performance and risk of stimulant use was observed both in girls and boys.

Conclusions: Relative age among classmates affects the academic performance of children into puberty, as well as their risk of being prescribed stimulants for ADHD. This should be taken into account when evaluating children's

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performance and behavior in school to prevent unnecessary stimulant treatment.

311. Off-Label Use of Octreotide in Infants

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Background: Data on the use and safety of Octreotide in the pediatric population is limited. A pilot study using an existing FDA device surveillance system, known as MedSun, was utilized to better understand Octreotide use in Neonatal Intensive Care Units (NICUs) and Pediatric Intensive Care Units (PICUs).

Objectives: To determine the pattern of use and adverse events in infants treated off-label with Octreotide.

Methods: Three MedSun facilities (and one additional facility) participated in a pilot study. A retrospective chart review was conducted.

Setting: Convenience sample of tertiary care children's hospitals in the United States from 2007 to 2010.

Exposure: Octreotide use in pediatrics.

Main outcome measures: Practice patterns, mortality, and other adverse events.

Results: Fifty-six cases were identified as having been treated with Octreotide. No patients had a primary diagnosis of hypoglycemia. The primary indication for therapy was chylothorax in 22/56 (39%) cases. The number of treated chylothorax cases decreased over time from 10 in 2007 to 5 in 2009. Thirty-one (55%) infants died during the observation period. Causes of death in this group of critically ill infants included multi-organ failure (11) and hypo plastic left heart syndrome (4). Information on adverse events was limited, and few were reported. Demographics: 44% females, median gestation age at birth 36 weeks, and median birth weight of 2.51 kg. The median weight at time of Octreotide administration was 4.0 kg and median age at administration was 2.0 months. Treatment trend over time revealed 78% of study subjects in 2007, 72% in 2008 to 45% in 2009 received continuous infusion. The median number of days of administration of the drug decreased from 10 in 2007 to 7 in 2008 to 1.5 in 2009.

Conclusions: This pilot study highlights the need for safety and efficacy information on Octreotide in children.

312. Soy Diet Influences the Expression of Estrogen Receptors alpha in Rat Ovary

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Background: The relatively recent use of soy and soy products in Western diet, has raised a concern among scientists, due to their estrogenic effect. Soy and its products are consumed by Asian people for centuries without any noticeable adverse reactions. They are also recommended for their beneficial effects, especially as natural hormone replacement therapy during menopause. Nevertheless, as phytoestrogens contained in soy act as weak estrogenic agonists/antagonists, they could influence the development of the reproductive system during crucial life stages like gestation, lactation and early age.

Objectives: The main objective of this study was to test the effect of soy diet on the expression of estrogen receptors alpha on rat ovary during early development.

Methods: Two groups of female Wistar rats 5 weeks old were used: the study group and the control group. The study group received ad libidum food enriched in soy protein during gestation, lactation and up to the age of 5 weeks. The control group received ad libidum the standard food during gestation, lactation and up to the age of 5 weeks. Both groups were grown under the same conditions and according to the rules of Good Laboratory Practice. The study was approved by the local Ethics Committee. After sacrifice, specimens of both ovaries were prepared for immunohistochemical examination by use of a monoclonal antibody against estrogen receptors alpha. The results were assessed by two different observers, blinded on the source of the specimen. Statistical analysis was performed with the statistical package SPSS.

Results: In the study group the expression of estrogen receptors alpha was lower in the germinal epithelium, the stromal cells and the thecal cells of the follicles and higher in the granulosa cells of the follicles, compared to the control group.

Conclusions: Soy diet during gestation, lactation and early age influences the expression of estrogen receptors alpha in rat ovary and it is possible to have an influence in the future reproductive life.

313. The Influence of Soy Diet on Rat Testis during Early Development

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Background: Soy and soy products are consumed by Asian people for centuries without any noticeable adverse reactions. Nevertheless, scientists are concerned about the recent use of soy products in Western diet, mainly because of their estrogenic effect. Although phytoestrogens contained in soy have minor estrogenic effects compared to estrogens, they could influence the development of the reproductive system during crucial life stages like gestation, lactation and early age.

Objectives: The main objective of this study was to test the effect of soy diet on the development of rat testes, during early development.

Methods: Two groups of male Wistar rats 5 weeks old were used: the study group and the control group. The study group received ad libidum food enriched in soy protein during gestation, lactation and up to the age of 5 weeks. The control group received ad libidum the standard food during gestation, lactation and up to the age of 5 weeks. Both groups were grown under the same conditions and according to the rules of Good laboratory Practice. The study was approved by the local Ethics Committee. After sacrifice, specimens of both testes were prepared and stained for microscopic examination and were assessed by two different observers, blinded on the source of the specimen. Statistical analysis was performed with the statistical package SPSS.

Results: There was no important difference on the basic histological structure of the young rat testis between the study and the control group. The seminiferous tubules, the seminiferous epithelium and the interstitial cells had no basic differences in both groups. The number of spermatocytes and the density of interstitial cells seemed slightly lower in the rats fed with soy during gestation, lactation and early age.

Conclusions: Soy diet during gestation, lactation and early age does not seem to have important effects on the basic structure of the rat testes, although it may influence the number of spermatocytes and interstitial cells of the testes.

314. The Treatment of Teething Symptoms: Observational Study of Pediatricians in Real-World General Practice

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Background: Teething is a natural occurrence of childhood, usually beginning at around 4 months and continuing until the age of 2 years. However, there is no existing consensus regarding the symptoms attributable to teeth development and guidelines for their treatment.

Objectives: The objective of this study was to describe what teething symptoms physicians actually ascribe to teething and their management of those symptoms in real-life medical practices.

Methods: We conducted a prospective observational study where a randomly selected 500 French pediatricians were asked to fill out case reports of the first four 3–24 month old patients they treated for teething. Of these, 161 agreed to participate and filled out case reports of medical and treatment data for 597 children at baseline. If the doctor considered follow-up necessary, medical data was also collected at day seven (n = 283 children).

Results: The median age was 8 months, 58.5% were male and for 49.8% of them it was the first teething experience. The average number of symptoms at the inclusion visit was 4.9 with the main symptoms including: gums tumefaction (80.6%), sialorrhea (78.9%), and unusual agitation/irritability (64.3%). At baseline, 35.7% of the children were treated by homeopathy alone, 35.5% with homeopathy in association with teething gels and 28.8% with teething gels alone. Children were also prescribed oral pain reliever/fever reducer (68.8%), mainly on demand. The treatments were mostly prescribed according to existing symptoms (62.9%), on parents' request (31.4%) or for both reasons (5.4%). Of those who had a follow-up visit, 67.4% still had disorders associated with teething, but severity of symptoms had decreased.

Conclusions: The study results provided us with a helpful overview of teething management in real life practice. French pediatrician's treat teething based on symptomatology, hence management is on a case-by-case basis.

315. Spirometry Testing in a Population of Italian Asthmatic Children

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Background: Although international asthma guidelines emphasize the importance of spirometry testing at least

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every 1–2 years in order to assess airway function, these recommendations are worldwide far from be applied.

Objectives: To estimate how many asthmatic children underwent spirometry in 1 year in the Lombardy Region, and to evaluate differences in socio-demographic determinants.

Methods: Data were retrieved from the administrative databases that store all pharmacological and diagnostic prescriptions issued to individuals living in the Lombardy Region. The analysis involved prescriptions dispensed during 2008 to the 6–17 year olds (1,047,241 subjects) living in Lombardy Region (15.4% of respective Italian population). The youths were identified as potential asthmatics (PA) when receiving age-appropriate formulation of anti-asthmatic drugs (R03 main therapeutic group of the Anatomical Therapeutic Chemical classification system), according to a previously validate criteria. Number of PA subjects having ≥1 spirometry claims was calculated, and factors associated with the probability of undergoing spirometry were evaluated by multivariate analysis.

Results: A total of 40,528 (3.9%) PA subjects was identified. In all, 70% of potential asthmatics received short-acting ß2 agonists (SABA) and 81% received a controller medication, in particular fixed associations of inhaled steroids (ICS) and long-acting ß2 agonists (LABA) (42%) or ICS alone (39%). Only 30% of PA underwent ≥1 spirometry during 2008, with differences between local health units (range 21–40%). The percentage increased with the degree of drug use, from 26% in occasional users (1 box only) to 35% in PA receiving more than 4 boxes. After adjusting for age, gender, place of residence and degree of antiasthmatic use, the chance of undergoing spirometry was greater in boys than in girls (OR = 2.3).

Conclusions: A low percentage of asthmatic children performed at least one spirometry during 1 year period. Moreover, demographic differences were found. This study highlighted a low compliance with the guidelines in the use of spirometry, suggesting that more appropriate management of asthma in childhood is needed.

316. Effectiveness of Palivizumab in Respiratory Syncytial Virus Prophylaxis in Children with Cystic Fibrosis

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Background: Evidence on the effectiveness of respiratory syncytial virus (RSV) immunoprophylaxis with palivizumab in children with cystic fibrosis (CF) is lacking. It is further unclear whether CF increases the risk for RSV infections in young children.

Objectives: To evaluate palivizumab effectiveness in children with CF.

Methods: We utilized Medicaid Extract files from 27 states (1999–2006) and the National Cystic Fibrosis Registry to establish a cohort of children 0–2 years with CF diagnosis. Eligible children entered the cohort after CF diagnosis and after RSV season onset, and were followed until season end, 2nd birthday, death, or hospitalizations for reasons other than the study outcome. Two outcomes were examined: hospitalization for RSV infections (RSV-ha), and hospitalization for acute respiratory infections potentially associated with RSV (ARI-ha). Palivizumab exposure was defined based on pharmacy or procedure claims as current (claim date plus 30 days), former (day 31–60 after a claim), and no exposure (days before the first or >60 days after any claim). Both outcomes were examined in a Cox regression model, adjusting for RSV risk factors and CF severity via exposure propensity score.

Results: The matched cohort included 1,974 infants (2,875 infant-seasons), who experienced 32 RSV-ha and 145 ARI-ha (3.9 and 17.9 per 1,000 season-months, respectively). Compared to periods of no use, the adjusted hazard ratio for current use was HR = 0.57; 95% CI 0.20–1.60. ARI-related hospitalizations showed a HR = 0.79 (95% CI: 0.50–1.23). Each month of increasing age reduced the ARI-ha by 5.8% (95% CI: 3.1–8.4).

Conclusions: RSV hospitalization incidence was low suggesting either little contribution of the virus to respiratory infections in CF patients or lack of RSV testing. Hospitalizations for acute respiratory illness showed no or minimal association with palivizumab use. Age greatly affected infection risk.

317. National Trends in Ambulatory Care Visits for Acute Otitis Media in Children under 5 Years of Age in the US

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Background: The seven-valent pneumococcal conjugate vaccine (Prevnar®, PCV7) was approved in the United States (US) in 2000 for active immunization against invasive disease and acute otitis media (AOM) caused by serotypes in the vaccine, starting at approximately 2 months of age. Before the introduction of PCV7 in the US, AOM accounted for approximately 24.5 million visits and up to $5.3 billion in annual treatment costs. Prior studies have demonstrated a reduction in visit rates for AOM after PCV7 among children <2 years in US using data through 2004.

Objectives: To assess the change in ambulatory care visit rates for AOM before and after introduction of PCV7 through 2009 among children < 5 years in the US.

Methods: This ecologic study evaluates trends in office and emergency room visits made by infants and children < 5 years for AOM during pre- (1994–1999) and post- (2001–2009) PCV7 periods using National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data. Annual and weighted average annual visit rates were calculated. Tests for trend were conducted using weighted least-squares regression for visit rates for children under 2 years and 2 to < 5 years of age. Mean visit rates in the stable pre- and post-PCV7 periods were compared.

Results: Trend analyses demonstrated that 1994–1998 and 2002–2009 were the stable pre- and post- PCV7 periods in both age groups. During the two stable periods, mean visit rates declined from 138 to 92 visits per 100 children < 2 years, and 55–45 per 100 children 2 to < 5 years. Among children < 2 years, the rate ratio of post- to pre-PCV7 (stable) periods was 0.67 (95% CI: 0.59, 0.75) representing a 33% reduction in AOM visit rates. Among children 2 to < 5, a rate ratio of 0.81 (95% CI: 0.71, 0.92) was observed, representing a 19% reduction in AOM visit rates between the two periods.

Conclusions: Significant reductions in ambulatory care visit rates for AOM were observed among children < 5 years in US after introduction of PCV7 during an extended follow-up period through 2009. The observed reduction was most marked among children < 2 years.

318. Analysis of ADHD (Attention-Deficit/Hyperactivy Disorder) among Flu-Vaccinated Pediatric Population in the United States Medical Claims Database

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Background: To better understand the reports of ADHD after the flu vaccinations in adolescence, an US clalims database study was planned.

Objectives: The purpose of this study was to describe the rates of ADHD before/after the index date of flu vaccination among adolescent population in the 2009 Thomson Reuters MarketScan® Commerical and Encouters Research Databases.

Methods: The flu vaccination groups were defined by ICD-9 CPT codes: 90655–90658 and 90650 for TIV (trivalent inactivated influzenza vaccine) and LAIV (live attenuated influenza vaccine), respectively. The conditions of ADHD were defined by ICD-9 diagnosis codes (314.0). The unvaccinated group "a" and "b"was defined as subjects who have "not had 'and "had" any medical/pharmacy claims recordered for any types of health care utilizations during the 3 months prior to the flu season (July 1st–September 31st), respectively.

Results: During 2009, the LAIV vaccinated only boys aged 9–18 years has the higher rates of ADHD (1–30 days before: 51.5 per 1,000 person-month vs. 1–30 days after: 68.0 per 1,000 person-month) than the TIV vaccinated only boys of similar ages (1–30 days before: 13.1 per 1,000 person-month vs. 1–30 days after: 43.6 per 1,000 person-month). Among the 2 unvaccinated groups, the unvaccinated "a" boys aged 9–18 years has slightly lower rates of ADHD (1–30 days before: 11.3 per 1,000 person-month vs. 1–30 days after: 12.7 per 1,000 person-month) than the unvaccinated "b" boys of similar ages (1–30 days before: 17.2 per 1,000 person-month vs. 1–30 days after: 21.3 per 1,000 person-month).

Conclusions: In conclusion, the limitations with claims database analysis such as parenting-preferences/physician-preferences in chosing/deciding health care options specially for the pediatric population which can not be measured as channelling bias may have confounded the results. Alternative approach such as self-control comparsions before/after the index date of flu vaccination are planned as the next step to explore the current findings further.

319. Pediatric Cancer Registries in North America and Europe

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Background: Recent EMA and FDA regulation require the development of pediatric drug development plans, increasing the need for epidemiologic data. However, compared with adults, pediatric cancers are rare and datasources are less readily available. An understanding of available pediatric cancer datasources with incidence and survival data would aid strategic decision making and trial planning.

Objectives: To review and determine publically available, online pediatric cancer registries in North (N) America and Europe.

Methods: English-language registries were identified through a web-based search and a PubMed literature review. These were evaluated across 6 criteria: use of the International Classification of Childhood Cancer (ICCC) coding, recent data (< 5 years), incidence, survival, data for ages ≤18, and ability to query data online.

Results: Five regional registries were identified: the Automated Childhood Cancer Information System (ACCIS, 35 countries in Europe), Surveillance Epidemiology and End Results Program (SEER, USA), National Program of Cancer Registries (NPCR,US), Canadian Cancer Registry (CCR, Canada), and Globocan (global). All provided incidence (counts and rates) and could be queried

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online. Three registries used ICCC codes. All described incidence among children and adolescents except Globocan (< 14 years). Three registries reported survival data. All had recent data except for ACCIS (1988–1997), but an update is expected. SEER was the only registry to meet all criteria; it also had staging where applicable.

Conclusions: National and regional registries have useful high-level pediatric incidence data. ACCIS, SEER, and NPCR met most of the above criteria. Details on stage, relapse, and other characteristics would further assist decision-making. Improved online querying capabilities and the standardization of information (age, ICCC coding) would assist analyses and cross-country comparisons. A similar evaluation of cancer registries in Asia is on-going.

320. Burden of Mental Disorders in Childhood Estimate Using Administrative Health Data

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Background: An increase in the prevalence of mental disorders in children and adolescents has been observed in the last few decades. Several studies have been performed, providing different estimates, depending on the geographical setting, the age range, and the tools used for the diagnosis.

Objectives: To estimate the burden of mental disorders in a representative Italian pediatric population using administrative databases.

Methods: The population target was 1,616,268 children and adolescents under 18 years living in the Lombardy Region, Italy. Three administrative databases were analysed to identify children with psychiatric disorders: a drug prescription, a hospital discharge form, and an outpatient ambulatory visit database. A youth was defined as a case if during 2008 he/she received at least one psychotropic drug prescription or was hospitalized for a psychiatric disorder (International Classification of Disease 9th revision codes 290–319), or attended a child neuropsychiatric outpatient unit for a visit and/or a psychological therapy intervention at least once. Epileptic children were excluded.

Results: In all, 63,550 youths (39.3 per 1,000; 95% CI 39.1–39.7‰) were identified as users of health care resources for a putative mental disorder. The prevalence was higher in boys than in girls (47.0‰ vs. 31.3‰) and the highest value was recorded in children 8 years old (60.2‰). A total of 59,987 youths (37.1‰) attended an outpatient child and adolescent neuropsychiatry service at least once, 3,605 (2.2‰) were admitted to hospital, and 2,761 (1.7‰) received at least one psychotropic drug prescription, 62% of which received antidepressants, 38% antipsychotics and 6% drugs for attention deficit hyperactivity disorder. Of 195 youths were prescribed more than one psychotropic drug class. In all, 57% of psychotropic users did not attend a child neuropsychiatry service.

Conclusions: The proportion of youths who received care for mental disorders in the Lombardy Region seems lower than in other countries. However, the fact that many children were prescribed psychotropic drugs without the supervision of a child psychiatrist is a reason for concern.

321. Results of Testing the Linkage of the Vaccination Registration Praeventis with the IPCI Medical Record Database in the Netherlands

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Background: Secondary use of health care data may advance medical knowledge especially with regard to disease etiology and outcome. Extending linkages between databases will be a major tool for knowledge discovery in the area of vaccine effectiveness and safety.

Objectives: Study the minimal amount of information necessary for linkage the national vaccination registry Praeventis to a large, well-established population-based medical record database i.e., IPCI.

Methods: A probabilistic linkage was established between the Integrated Primary Care Information database, comprising the medical records of more than 1 million subjects, across various regions in the Netherlands and the nationwide Praeventis databases. Praeventis captures information on the childhood immunization program for all citizens, currently until the age of 18 years.

Results: A high percentage of children from 1 to 18 years of age were linked well (range 79.1–86.2%). After that age, the linkage percentage dropped down (range 0.7–7.8%) because Praeventis does not keep addresses up-to-date for children not included in the National Vaccination Program. A rise in linkage percentage is seen from 25 to 40 years of age, which is caused by including pregnant women in Praeventis (range 6.6–25.2%). After that age, the linkage percentage decreased from 8.8% on the age of 42 years to 0 for people of 50 years and older.

Conclusions: The quality of linkage children based on birth date and postal code is high. Only for twins, additional information (f.e. first character of the first name) is

necessary. The next step will be to test the association between MMR vaccination with febrile convulsions (true positive association) and fractures (true negative association). When this linkage is successful, the safety of vaccinations may be monitored using this linkage method.

322. Agreement between Parental-Reported Usage and Dispensed Asthma Drugs in Children. A Comparison between the BAMSE-Cohort and the Swedish Prescribed Drug Register

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Background: Asthma is one of the most common diagnoses for children with a prevalence of approximately 10%. The knowledge about drug use among children is limited with uncertainties about the validity depending on data sources used.

Objectives: The aim of this study was to investigate how well parental reported use of asthma drugs in a questionnaire corresponded with register data on dispensed drugs.

Methods: Data on parental reported use of asthma drugs from 3,366 children (12–14 years old) in a population-based birth cohort in Stockholm, Sweden (the BAMSE-cohort) were compared with data on dispensed drugs from the Swedish prescribed drug register. The questionnaires were answered between the 3rd of April and the 7th of December 2008 and contained information on drug use during the last 12 months. Using the parental-reported data as reference, sensitivity and specificity with 95% confidence intervals were computed for different antiasthmatic drugs, applying fixed-time windows of 12 and 18 months and "ever" in the prescribed drug register. Ever was defined as a drug disposed any time before the date of the questionnaire back to the start of the register in July 2005.

Results: According to the questionnaires 10.7% of the children used an asthma drug during the preceding 12 months compared to 7.1% in the drug register. The sensitivity of the register was 69.2% (95% CI 63.7–74.4) and the specificity was 98.1% (97.3–98.7) when using a 12 month time window. When the time window was expanded to 18 months the sensitivity increased to 79.9% (74.9–84.3) while the specificity decreased to 97.0% (96.0–97.7). When using the time window ever, the sensitivity was 90.9% (95% CI 87.1–94.0) and the specificity was 92.6% (95% CI 91.3–93.9).

Conclusions: The concordance between the questionnaires and the Swedish prescribed drug register was relatively high. The sensitivity and specificity indicated that a time window with 18 months ought to be preferred when using register data to assess the use of asthma drugs in children.

323. Impact of Maternal Attachment on Infant Development at 1-Year of Age: Results from the OTIS Antidepressants in Pregnancy Study

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Background: A poor mother-infant attachment has been associated with chronic pediatric health problems and suboptimal psychological and cognitive development.

Objectives: To evaluate the impact of maternal attachment on the cognitive and socio-emotional development of infants at 1-year of age whose mothers were suffering from depression or anxiety.

Methods: The OTIS Antidepressants (AD) in Pregnancy Study cohort was used. Women were recruited through 9 North American Teratogen Information Services and the outpatient obstetric clinic of CHU Ste Justine (Montreal). To be included, women had to be >18 years old, <15 weeks pregnant, and not using known teratogens. They were followed throughout pregnancy until 12-months postpartum. Maternal attachment, cognitive and socio-emotional development were assessed at 12 months postpartum using the Maternal Attachment Postnatal Questionnaire (MAPQ), the problem-solving scale of the Ages and Stages Questionnaire (ASQ) and Bayley-III socio-emotional scale, respectively. Socio-demographic and lifestyle data, depressive symptoms (using the EPDS),

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AD medication use and other potential confounding variables were collected through telephone interviews. Logistic and linear regression models were built to assess, at 1-year postpartum, the association between maternal attachment and cognitive development and between maternal attachment and socio-emotional development, respectively.

Results: Overall, 206 mother-infants pairs were included. The MPAQ and th ASQ were administered to all the mothers and infants, respectively. A subset of 94 babies completed a socio-emotional development evaluation using the Bayley-III scale. Adjusting for potential confounders, optimal maternal attachment was significantly associated with decreasing the risk of delay in problem-solving skills at 1-year of age (AOR = 0.87; 95% CI [0.76; 1.00]); it was also positively and significantly associated with the socio-emotional development at 1-year of age ($p = 0.02$).

Conclusions: These results suggest that optimal maternal attachment protects infants with regards to early cognitive development and improves their socio-emotional development.

324. Pediatric Epidemiological Study for Chronic Hepatitis B (CHB)

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Background: In order to conduct robust, interventional clinical studies in the CHB pediatric population, it is important to have a comprehensive understanding of the disease and the epidemiology in this population group, as children exhibit a markedly different disease course than adults.

Objectives: Our aim was to describe demographics, transmission, current disease characteristics and treatment history in children and adolescents with CHB in Asian and Western countries.

Methods: This multi-center, observational, cross-sectional study collected epidemiological data from CHB patients aged 2–18 years. Data was collected anonymously from 1640 pts at 80 sites in Asian and Western countries.

Results: Asia represented 59% of the total study population. In all countries, the majority of pts were older than 7 years and between 13 and 18 years of age (53%). The mean age was 11.8 years. Mean age at first diagnosis of HBV was higher in Asian countries (8.6 years) compared to Western countries (4.6 years). Mother to child transmission (MTCT) was higher in Asian countries (44.6%) than in Western countries (27.7%). Decompensated liver disease was found in a very small percentage of participants (0.8%). In Asian countries, 59% of pts were HBeAg+ and 24% were HBeAg-. In Western countries, 48% of pts were HBeAg+ and 44% were HBeAg-. In Asian countries, 57.1% of pts with MTCT HBV were vaccinated for HBV and 25.4% received HBIG. In the Western countries, these figures were 43.1% and 12.8%, respectively. A higher proportion of Western pts (42.3%) had previously received treatment compared to Asian pts (7.1%). In the 2–6 years age group, most pts from Asian and Western countries had not received any treatment (94.8% and 91.0%, respectively).

Conclusions: In this large worldwide epidemiological study in children and adolescents, differences in pts characteristics were reported between Asia and Western countries. The mean age of diagnosis was higher in Asia. The majority of Asian pediatric CHB pts were infected through MTCT. Conducting future pediatric clinical trials in decompensated CHB and in children below the age of 7 years is projected to be increasingly more difficult due to the declining prevalence.

325. Male/Female Incidence Ratio of ADHD Drug Treatment in the Netherlands from 2000 Until 2010

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Background: ADHD has become a much debated topic in the last few years. More attention and awareness for ADHD has led to an increase in incidence. Especially awareness for the subtype of ADHD were patients, mostly females, demonstrate predominantly inattentive symptoms, has increased.

Objectives: To determine the male/female incidence ratio of ADHD drug treatment in the Netherlands from 2000 until 2010.

Methods: From the PHARMO database, including amongst others, drug dispensing records of approximately

3.2 million inhabitants in the Netherlands, we selected patients with a first dispensing of ADHD medication including methylphenidate, atomoxetine and dexamphetamine in the period 2000–2010. For each calendar year, the male/female incidence ratio of ADHD drug use was determined by dividing the incidence among males by the incidence among females. Results were stratified by age groups.

Results: Overall, the male/female incidence ratio of ADHD drug treatment decreased from 3.4:1 in 2000 to 1.6:1 in 2010, meaning a growing proportion of female patients. The largest decrease in the male/female ratio was observed among adolescents (13–18 years: from 4.5:1 in 2000 to 1.6:1 in 2010), followed by 9–12 year-olds (from 5.5:1 in 2000 to 2.7:1 in 2010) and 0–8 year-olds (from 6.2:1 in 2000 to 3.5:1 in 2010). Among adults and seniors this ratio fluctuated from 0.9:1 to 2.1:1. Although the incidence among females has increased more over the years, the incidence among males remained higher throughout the study period.

Conclusions: This study shows that the proportion of female patients starting ADHD drug treatment is increasing. This in line with the increased awareness of ADHD among females.

326. Increase in Psychotropic Drug Use between 2006 and 2010 among Adolescents in Norway: A Nationwide Prescription Database Study

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Background: Overall, studies on psychotropic drug use among adolescents are scarce and do not give any detailed information on their use pattern over time by age, gender, psychotropic subgroups and long-term use.

Objectives: The purposes of this study were to investigate the prevalence of psychotropic drug use among adolescents aged 15–16 during 2006–2010 related to gender and subcategories of psychotropic drug, and to study long-term psychotropic drug use (2007–2010) among incident psychotropic drug users in 2007.

Methods:

Longitudinal register study: This study is based on information retrieved from the nationwide Norwegian Prescription Database for the period 2006–2010.

Participants: The study population consisted of adolescents aged 15–16 years who had filled at least one prescription for a psychotropic drug in 2006, 2008 and 2010.
Main outcome measures: Filling of psychotropic drug prescriptions.

Results: Overall, psychotropic drug use increased from 9.3 to 17.3 per 1000 among boys and 11.7–17.4 per 1,000 among girls during 2006–2010. During the same period, hypnotic drug use increased from 1,338 (10.5 per 1,000) to 2,221 (17.3 per 1,000) and its prevalence increased in both genders – among boys nearly doubling from 9.3 to 17.3 per 1,000 and among girls from 11.7 to 17.4 per 1,000. Melatonin accounted for most of this increase. For melatonin, the annual median amount dispensed was 180 DDDs through the period until 2010, when it decreased to 90 DDDs. Sixteen percent of all incident psychotropic drug users in 2007 had still prescriptions dispensed in 2010.

Conclusions: This study shows an increase in psychotropic drug dispensed among adolescents in Norway, mainly attributed to the increasing of melatonin. The amount of melatonin dispensed indicates more than sporadic use over longer periods, despite that the use is licensed for 55 years or older in Norway. Antidepressants were dispensed more frequently among the girls, compared to the boys. Thus, evidence about efficacy of psychotropic drugs in general, and melatonin in particular, in adolescents is warranted.

327. Differences in the Prescribing Behavior of Oral Contraceptives in Adolescents and Adults

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Background: Oral contraceptives (OCs) are a very popular method of reversible birth control and are widely used by adolescents and adults because of the easy administration and additional beneficial effects. The International Active Surveillance Study – Safety of COntraceptives: Role of Estrogens (INAS-SCORE) is conducted in 7 European countries and the USA.

Objectives: To ascertain differences in adolescent and adult OC users, who are representative of the actual user population with regard to demographic and risk factors.

Methods: The INAS-SCORE study is a prospective, controlled, non-interventional cohort study, which started in seven European countries (Austria, Germany, France, Italy, Poland, Sweden and the UK) and the USA in 2009. Women being prescribed a new OC are recruited by a network of prescribing physicians. Baseline information includes questions on a variety of data, e.g., information about demographic data, history of OC use and medication.

Results: Until now, 35,255 women were enrolled into this study, of which 3,170 are girls below 18 years of age. Adolescents have a lower mean BMI (22.0) compared to the adult study population (24.3) and are less obese with a BMI of 35+ (1.4% compared to 5.4%). Minor differences exist in the smoking behavior: 20.2% of the adoles-

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cents are smoker (1.5% with >15 cig./day) compared to 23.6% of the adult study population (3.5% >15 cig/day). Adolescents are more frequently users of regular medication (25.0%, adult study population: 20.2%), the major category is medication for the nervous system, which is used by 7.9% of the adolescents compared to 6.3% of the adult study population. Of these, psychotropic medication is widely used by OC users below the age of 18 years (7.1%) compared to the adult study population (4.3%). Recruitment is still ongoing. Updated results will be presented at the meeting.

Conclusions: Overall, demographic risk factors vary in the two user populations. Some of which can be explained by the age difference (e.g., BMI and obesity), others are different than expected (higher medication use in adolescents, especially psychotropic medication).

328. Phenotypic Spectrum of Hematological and Visceral Disease in Type 3 Gaucher Disease and Response to Imiglucerase Therapy: Preliminary Analysis from the ICGG Gaucher Registry

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Background: Patients with type 3 Gaucher disease (GD3) develop neurological manifestations in infancy or childhood. Enzyme therapy with alglucerase/imiglucerase has been used to treat the hematological and visceral manifestations of GD.

Objectives: To define the phenotypic spectrum of hematological and visceral disease in patients with GD3 and its response to alglucerase/imiglucerase therapy.

Methods: All patients <18 years of age who were enrolled in the ICGG Gaucher Registry as of July 2010 with a diagnosis of GD3 were included in this analysis. Subsets of patients with baseline status of anemia, thrombocytopenia, splenomegaly, hepatomegaly, or height z-score ≤-1 were identified. Outcomes of changes from baseline in hemoglobin concentration, platelet count, and hepatic and splenic volumes and height Z-scores were assessed up to 5 years following initiation of therapy using non-linear mixed effects models.

Results: A total of 334 GD3 patients were identified; the majority of patients were from the Middle East (34%), Europe (29%) and the USA (16%). Ninety percent of patients were diagnosed at age <6 years and 81% of patients initiated therapy at age <6 years. Mean baseline height Z-score was -2.7 among the subset of patients with height Z-score ≤-1 at baseline (n = 159). Improvement in growth was seen after both 1 (mean height Z-score -2.5) and 5 years of treatment (mean height Z-score -1.7). Among patients with baseline anemia (n = 145), anemia was present in 42% within ≤1 year of treatment initiation, and declined to 29% after 5 years of treatment. For patients with baseline thrombocytopenia (platelet counts $< 120 \times 10^3/mm^3$) (n = 131), thrombocytopenia was present in 57% within <1 year, and declined to 11% after 5 years of treatment. Liver and spleen volumes decreased over the 5 years of treatment.

Conclusions: At treatment initiation, there was onset of prominent visceral and hematologic disease manifestations in GD3 patients before the age of 6 years and the patients exhibited striking growth failure. These effects were generally reversed by alglucerase/imiglucerase treatment within 5 years.

329. Marketing, Prescribing and Dispensing of Methylphenidate in Belo Horizonte, Minas Gerais, Brazil

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Background: The Attention Deficit Disorder with Hyperactivity/Impulsivity (ADHD) is a persistent pattern of inattention and/or hyperactivity more intense and frequent than usual in children. The preference for medical treatment lies with methylphenidate, a psychostimulant similar to amphetamine, and the use is growing all over the world. Methylphenidate is classified as a psychotropic substances and subject to the control marketing. Its use has become very popular and there are suspicions about the rationality of their consumption.

Objectives: To analyze the characteristics of the consumption of methylphenidate in Belo Horizonte on legal, clinical and epidemiological studies in 2006.

Methods: In a cross-sectional study, through the analysis of bulletins of sales control of and of prescriptions notifications, we characterized aspects of its use in Belo Horizonte, Minas Gerais: sex, DDD, PDD, length of the treatments prescribed, the dispensation average period and others.

Results: We calculated a defined daily dose (DDD) of 0.37/1000 inhabitants/day and a prescribed daily dose (PDD) of 23.9 mg/day (10–240 mg/day). The average

length of the treatments prescribed was 31 days (max. 600 days), the dispensation was made for an average period of 29 days (max. 540 days) and spending on consumption was estimated as $ 725,000. The consumption was higher in areas of the city economically favored, with a remarkable number of formulations which ease the abuse and harden treatment adhesion. The prescribing and dispensing of methylphenidate did not accomplish with all pharmacotherapy and legal requirements.

Conclusions: The results emphasize the importance of controlling and supervising sales of methylphenidate. We also highlight the need to redirect its use in the line of the concept of rational use of medicines.

330. Review of All Products Authorized by the European Medicines Agency from 1995 to 2011 in Regard to Pediatric Investigation Plan Applications

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Background: Pediatric Investigation Plans (PIPs) were introduced by the European Commission in January 2007 to help ensure that medicines for children are included in the mainstream drug development process in Europe.

Objectives: The objective of this study was to review all authorized products by the European Medicines Agency (EMA) from 1995 to 2011 to identify (1) those with a potential pediatric indication, and (2) those with a PIP application.

Methods: On the EMA website, the European Public Assessment Reports (EPARs) were searched manually. For each product, the Summary of Product Characteristics (SmPC) was reviewed to explore quotes relative to any potential pediatric indication. The products were distributed in four categories: C1 = adult indication only, C2 = safety/efficacy not studied in children, C3 = adult and pediatric indication, and C4 = pediatric indication only. For each product, the EMA pediatrics database was searched for PIP applications.

Results: Of 633 products were authorized by the EMA (281 in 1995–2006, and 352 in 2007–2011). From 1995 to 2006, 33.53% of the authorized products presented a lack of evidence in the pediatric population and 57% of the products in the period of 2007–2011. In total, 746 PIP applications were identified (products authorized and under development). A PIP was requested for 21.4% of the products authorized before the regulation (1995–2006) and for 19% of the products authorized after the EU pediatric regulation of 2007.

Conclusions: The categorization of authorized products according to the SmPC quotes has shown that many products had potential pediatric indications needing confirmation through new research programs. As expected, most of the PIP applications concern products under development. However, it is interesting to note that almost 20% of the requests concern authorized products, with a higher percentage of requests for products authorized before the pediatric regulation. These findings suggest that the pediatric regulation in Europe is fostering pediatric research to create more therapeutic options for children and healthcare providers.

331. A'TEAM: Atopy' Therapeutic Education Assessment Measure: A Tool for Evaluating Therapeutic Education in Atopic Dermatitis

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Background: The most recent studies have estimated that the prevalence of atopic dermatitis in children aged between 6 /7 is 8%, and 10% in children aged between 13/14. In European countries, questionnaire studies showed prevalence varying between 7 and 28%, whereas medical exam studies placed it between 6 and 16%.

Objectives: Evaluate the impact of TEP offered, by asking the question: Does the proposed educational program achieve its objectives?

Methods: Care given to patients during an atopic eczema flare-up aims to reduce inflammation and pruritus in order to relieve the patient and avoid secondary infection. The application of a topical corticosteroid, an antiseptic solution and a local antibiotic, possibly combined with antihistamines as a complement, can help the young sufferer better cope during flare-up stages. Skin dryness should be treated with emollients, avoiding irritating substances such as soaps. These different elements (prevalence, management) have contributed to the emergence of therapeutic education for patients (TEP). TEP can be offered by non-dermatologist health professionals.

Results: The questionnaire is composed of 3 sub-questionnaires designed to assess the burden on the family when managing atopic dermatitis, the degree of severity of the condition (PoScorad) and the level of knowledge of the pathology. To evaluate the degree of severity the PoScorad is self-evaluating; For the burden, the questionnaire is completed; the ratio of burden compared to QoL is assessed by taking into account the general daily disability created by the disease (social, financial). The same questionnaire is completed by each parent before they take part in education sessions, after having completed their first 3 sessions, after a cycle of sessions and 6 months after. This relatively long-term evaluation period allows us to answer the question of sustainability of therapeutic education's benefits.

Conclusions: These 3 questionnaires cover precisely the area of TEP which should lead to both a clinical improvement and a lesser burden on the family by reducing flares

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and relapses and controlling dermatitis through better disease understanding.

332. Patterns of Topical Calcineurin Inhibitor Drug Use. Impact of Regulatory Actions in Off-Label Use

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Background: The topical calcineurin inhibitors (TCI) were approved in Europe as second line treatment for short-term, non-continuous treatment of Atopic dermatitis (AD) in adults and children >2 years old who failed to respond to conventional therapies such as topical corticosteroids (TCOR). In 2005–2006 the TCI benefit-risk profile was reviewed in view of its potential carcinogenicity and their off-label use, specially in children <2 years old. The product information was updated and additional measures to minimize risk were undertaken (safety warning,-direct heath professional communication).

Objectives: To describe the characteristics of patients treated with TCI and to evaluate the impact of regulatory actions on the potential off-label use of TCI.

Methods: A retrospective study was performed in a Spanish primary care database (BIFAP). Patients with a first prescription of TCI in the study period (2003–2009) were included in the study. Two periods were defined, pre-regulatory actions (2003–2004) and post-regulatory actions (2007–2009). The following indicators were compared between both periods: rates of new treatments in <2 years old;% patients with previous treatment with TCOR and% patients with recorded diagnosis of dermatitis/eczema.

Results: Of 23,893 new users of TCI were identified in the study period (pimecrolimus 15,823 [66.2%]; tacrolimus 8,070 [33.8%]). 56.8% were female and median age was 32 years (interquartil range 7–54). The proportion of treated patients <2 years old was of 8.1% whilst the percentage of registered dermatitis/eczema and previous TCOR use were of 54.6% and 58.2% respectively. The rate of new TCI treatments in <2 years significantly decreased between pre and post-regulatory actions periods (14.2–5.95 per 1000 patient-years respectively, $p < 0.05$). The proportion of patients with a previous treatment of TCOR and recorded diagnosis of dermatitis/eczema increased in the post-regulatory actions period (risk difference 12.1% and 2.3% respectively,$p < 0.05$).

Conclusions: Results suggest that regulatory actions had an impact in the decrease of the off-label use of TCI especially in patients <2 years old. Additional measures may be needed to improve the situation further.

333. The Use of GP Questionnaires to Assess Psoriasis Severity in The Health Improvement Network (THIN) Database

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Background: The natural course of psoriasis is not well described. To better understand this, data from The Health Improvement Network (THIN) database was used to capture detailed information on disease progression in psoriasis patients. Limitations of THIN data are that psoriasis severity, phototherapy and biologic prescriptions, and hospitalisations may not be recorded. Psoriasis Area Severity Index is often used to assess severity, but relies on GPs recording body surface area (BSA) affected. Phototherapy and biologics are usually prescribed in secondary care. We derived an algorithm using pre-collected THIN data to classify psoriasis severity and administered GP questionnaires to validate this. This abstract describes the proposed methodological approach.

Objectives: This study aims to describe the natural progression of psoriasis, using both pre-collected THIN data and GP questionnaires.

Methods: A retrospective cohort study, using THIN data, to describe the natural progression of psoriasis. Of 5,000 patients with an incident psoriasis diagnosis between 01/01/2004 and 31/12/2006 were included. Eligible patients had at least 3 years of data both before and after (unless died) diagnosis. From the pre-collected THIN data, patients were classified based on the 3 months following psoriasis diagnosis:

1. Mild-moderate: No treatment or topical treatments only.
2. Moderate-severe: Systemic therapy and/or phototherapy and/or biologics and/or hospitalisations for psoriasis.

GP questionnaires were administered to a random sample of 300 psoriasis patients (100 mild-moderate, 200 moderate-severe) to:

1. Obtain information on phototherapy, biologics and hospitalisations.
2. Assess psoriasis severity via collection of BSA affected.

Validity of the psoriasis severity classification algorithm will be assessed by contingency tables comparing the severity derived from the GP questionnaires with that from the pre-collected THIN data. Agreement will be assessed using Cohen's K coefficient.

Results: This abstract describes a methodological approach; there are no results to be presented.

Conclusions: GP questionnaires can be used to overcome some of the limitations inherent to pre-collected THIN data.

334. A Review of Stevens Johnson (SJS), Toxic Epidermal Necrolysis (TEN), and Erythema-Multiforme (E-M) Reports from the FDA AERS Database from 1968 to 2009

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Background: There is increasing interest in serious skin reactions associated with the use of pharmaceuticals. The FDA AERS database contains millions of reports and allows for a cross sectional analysis of all reports for a given event which are then stratified by drug, age, and sex. Typical pharmacovigilance is drug-centric and such a view may miss signals for rare events associated with classes of drugs. Event-centric reviews can provide insight into possible relationships not otherwise apparent.

Objectives: To quantify the reports of serious skin reactions (SJS, TEN, E-M) within the AERS database and to study drugs associated with these reports. To determine whether a review of all reports of certain events in the database can reveal possibly unknown associations.

Methods: Data from the FDA AERS system was selected from 1968 to 6/30/2009 for all reports of SJS, TEN, and E-M. For each drug associated with the study reports, the total number of reports for that drug were computed. For each report, the last best case was determined and the suspect status of the drug. Percentages of each event were computed. The data was further stratified by age and year. Because of differential reporting of nonserious events, these reports were excluded.

Results: AERS contains more than 24,000 study events. There are several drugs known to be associated with SJS, TEN, and E-M. The expected associations are apparent from the data. A review of all reports of these events, though, shows that there are some drugs that are less known and should be further investigated for a possible relationship.

Conclusions: Because of the size of the AERS database, it is possible to study all of the reports of certain events and then look to see if there are possible signals associated with various strata such as drug, age, and sex. Typical pharmacovigilance is drug-centric and may miss signals of rare serious events that may become apparent when event-centric analysis is performed. With respect to SJS, TEN, and E-M, these events are sufficiently serious to warrant such a review.

335. Screening Method for Association of a Drug to Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis Using a Claims Database

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Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are frequently related to medications, however it is hard to identify the culprit medication for SJS or TEN from a claims database.

Objectives: To develop an algorithm to search medication related to SJS/TEN.

Methods: The Korean Health Insurance Review and Assessment Service (HIRA) database from January 2005 to June 2006 was used. The database contained all insurance claims data including diagnosis and prescription for 4 million elderly Koreans who were older than 65 years. Cases were defined as those with any claims of SJS (ICD-10: L51.1) and TEN (L51.2 or T50.9), and the date of the first claim was the index date. We classified medications into 8,716 general names following codes of HIRA formulary. We used the case-crossover design to evaluate the association of each medication to SJS/TEN, in which exposure to the a certain medication in a 1 week window period prior to the diagnosis of the SJS or TEN was compared to the exposure to that medication in 4 earlier 1 week control periods. Conditional logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) and we corrected the p-values from multiple comparisons using a false discovery rate. p-Value < 0.05 were considered to be significant and the labels of medication with significant association were reviewed for SJS/TEN.

Results: We identified 296 patients with SJS and 60 with TEN. After screening of 8,716 medications, we found 144 medications associated with SJS/TEN ($p < 0.05$), and 29 of them were labeled for SJS/TEN. Anti-microbials ($n = 20$) and analgesics ($n = 10$) were the most frequently related drug classes.

Conclusions: Large automated databases like electronic health records, claims database will be helpful resource to supplement spontaneous reporting data by overcoming limitation of under-reporting and utilizing clinical information. Further effort to avoid indication bias which is specific to SJS/TEN and to validate the outcome would be indispensable.

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336. Integrating Patient-Reported Outcomes (PRO) and Medical Record Data (MR) in Observational Studies: Results from a Direct-to-Patient Pilot Study in Gout

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Background: The growth in on-line patients has given rise to new direct-to-patient research methods (i.e., recruitment of patients without physician sites). One concern, however, is the absence of physician input to validate diagnosis and provide clinical data.

Objectives: The objective of this study was to employ a direct-to-patient approach to collect patient-reported outcomes (PRO) and medical record (MR) information.

Methods: In July 2011, a random sample of US MediGuard.org members age 18–80 were invited to participate via email based on the presence of a gout medication or diagnosis in their profile. Interested members clicked on an embedded link to access study information and screen for eligibility. The first 50 consenting participants continued to complete a survey and electronic and paper medical release forms. Paper forms were mailed to Outcomes Health Information Solutions to contact physicians and obtain participant charts. The primary endpoint was medical records collected; the secondary endpoint was confirmed gout diagnosis based on the MR.

Results: Of 120 members clicked on 1,250 emails sent (9.6%). Five members (4%) declined to participate due to the medical record requirement, although lack of interest could have been as high as 38% if all individuals closing the browser are included. Of the 50 participants who enrolled and completed the survey and electronic MR release, 42 (84%) returned the paper form. In total, 38 of 50 charts were obtained (76%): 28 of 38 (74%) with electronic and 10 of 38 (26%) with paper consent. Thirty-five of 38 MRs included a gout diagnosis and 2 MRs contained a gout medication. Only 1 MR was missing any mention of gout.

Conclusions: Patients can be recruited directly for observational study designs that include PRO and MR data with over 75% completeness. In this pilot, nearly all (37 of 38) charts confirmed patient-reported data. Results from this proof of concept suggest that it is possible to obtain observational data from the patient and provider in a more time and cost efficient manner.

337. Severe Cutaneous Reactions Requiring Hospitalization in Allopurinol Initiators: A Population-Based Cohort Study

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Background: Rare but potentially life-threatening cutaneous adverse reactions have been associated with allopurinol, but population-based data on incidence and mortality of such reactions are scarce.

Objectives: To evaluate incidence rate (IR) and in-hospital mortality of hospitalization for severe cutaneous adverse reactions (SCARs) in allopurinol initiators compared to non-allopurinol users and determine whether high-dose of allopurinol is associated with the risk of SCARs.

Methods: We conducted a propensity score-matched cohort study using data from five large Medicaid programs. The primary outcome was identified by the principal discharge diagnosis code 695.1 (erythema multiforme and related conditions). Cox proportional hazards model evaluated the relative risk of SCARs associated with use of allopurinol. Among the allopurinol initiators, HRs for high-dose (≥300 mg/day) vs. low-dose allopurinol were calculated after adjusting for potential confounders.

Results: During a follow-up period of 65,625 person-years for allopurinol initiators (n = 90,358), 45 were hospitalized with SCARs. The crude IR was 0.69 (95% CI 0.50–0.92) per 1,000 person-years. All 45 cases occurred within 365 days and 41 (91.1%) within 180 days after initiating treatment with allopurinol. Twelve (26.7%) patients died during the hospitalization. The crude IR in non-allopurinol users (n = 90,358) was 0.04 (95% CI 0.02–0.08) per 1,000 person-years. The risk of SCARs was increased in allopurinol initiators compared to non-users (HR 9.67, 95% CI 4.55–20.57). Among allopurinol initiators, the HR for the high- vs. low-dose allopurinol was 1.57 (95% CI 0.87–2.84) after adjusting for age, comorbidities and any recent diuretic use.

Conclusions: Among allopurinol initiators, SCARs were found to be rare but often fatal and occurred mostly in the first 180 days of treatment. The risk of SCARs was ten times as high in allopurinol initiators compared to allopurinol non-users.

338. Statins Do Not Influence Giant Cell Arteritis Outcome in the French APOGEE Cohort. A Population-Based Study Using the French Health Insurance System Database

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Background: Statins may prevent cardiovascular deterioration for Giant Cell Arteritis (GCA) patients.

Objectives: To investigate the potential relationship between exposure to statins, GCA occurrence and exposure to glucocorticosteroids (GCs) in a cohort of incident GCA patients.

Methods: The APOGEE cohort includes incident GCA patients of the Midi-Pyrénées County, from 2005 to 2008. GCA patients were identified in the French Health Insurance System (FIHS) database by ICD-10th codes of a chronic disease related to GCA. Incident cases were defined by a continuous GCs course lasting for at least 6 months, without any previous exposure to GCs during the 6 preceding months. Reference time (T0) was the date of first GCs prescription. For each case two age and gender matched-controls were randomly selected. The primary endpoint (PEP) was achieved when the patient reached a prednisone daily dose < 5 mg/day without any increase during 6 months. We investigated the influence of a sustained exposure to statins on GCA occurrence and on the primary end point by a multivariate Cox analysis.

Results: The cohort included 103 patients, (80 women (77.7%); mean age 74.8 (± 9) years; mean follow-up 48.9 (± 14.8) months; mean initial GCs dosage 54 (± 27) mg/day). Eighty-one (78.6%) patients reached the PEP at 24.3 (± 11.2) months and with a mean cumulative GCs dose at 11.4 (± 6.1) g. Twenty eight (27.2%) patients had a sustained exposure to statins in the 6 months before T0, which was similar to that observed among matched controls ($p = 0.29$). In the multivariate Cox analysis, a sustained exposure to statins before T0 was associated with a higher probability to achieve the the PEP (HR = 1.87 [1.16–3.03], $p = 0.01$). However, there was no influence of a sustained exposure to statins when it was included as a time-dependent covariate (HR = 1.06 [0.81–1.40], $p > 0.05$). The GCs cumulative dose among patients exposed to statins was not different from that delivered to patients not exposed ($p = 0.78$).

Conclusions: A sustained exposure to statins did not protect from GCA occurrence and was not associated with a reduced exposure to GCs.

339. Methotrexate Utilization in Rheumatoid Arthritis. Treatment Re-Starts after Gaps of at Least 90 Days

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Background: Methotrexate (MTX) is considered the best first-line drug for treatment of rheumatoid arthritis (RA). Compliance to MTX is considered generally good. Several studies have, however, shown that 50% of the RA patients discontinued MTX treatment after 5 years. For both osteoporosis and chronic gout, a compliance behaviour has been observed where patients frequently stop and restart their treatment. In RA, flare-up of disease activity is likely to occur if MTX treatment is paused. Therefore it would be useful to know if RA patients exhibit a compliance behaviour similar to that of patients with gout and osteoporosis.

Objectives: To describe the extent to which RA patients who discontinue MTX treatment later restart therapy, and to investigate predictors of restart.

Methods: A cohort study was conducted based on data from the Danish National Patient Registry and prescription data. MTX drug discontinuation was defined as a gap ≥90 days from the expiration of one MTX prescription to the redemption of a new one. Kaplan Meier estimates were used to compute the cumulative probability of resuming MTX treatment and Cox proportional hazard to estimate the hazard of treatment return. A case-crossover analysis compared the frequency of events that could have a transient effect on MTX restart.

Results: Among 788 patients, who started MTX, a total of 299 patients experienced a gap ≥90 days and 66% of these restarted treatment. The Kaplan Meier analysis showed that 50% of the patients had returned to treatment within 1.4 years. The case-crossover analysis showed concurrent treatment with corticosteroid and other disease-modifying antirheumatic drugs to be negatively associated with MTX restart. The Cox regression analysis showed that women compared to men, older patients, patients with the presence comorbidity, and patients with high disease activity were less likely to restart.

Conclusions: A large proportion of RA patients who discontinued MTX restarted treatment. The conditions determining treatment behaviour was, however, not clear and we suggest health care professionals routinely address MTX utilization in order to support patients in remaining continuous users.

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340. Risk of Serious Infection and Malignancy in Rheumatoid Arthritis Patients Treated with Anti-Tumor Necrosis Factor-Alpha Biologics

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Background: Treatment of rheumatoid arthritis (RA) with anti-tumor necrosis factor alpha (aTNF) biologics may increase risk of serious infection (SI) and malignancy due to their immunosuppressive effects.

Objectives: To estimate SI and malignancy rates in RA patients treated with aTNF biologics using a claims-based data source.

Methods: A retrospective cohort study of RA patients initiating treatment with adalimumab (ADA), etanercept (ETN), or infliximab (INF) from January 2000–December 2008 was conducted using an administrative claims database. Patients were followed for SI and malignancy. Incidence rates (IRs) per 1,000 person-years (PYs) were calculated for each aTNF using time-on-drug analysis based on current aTNF biologic exposure status for SI and intent-to-treat analysis based on the initiating aTNF biologic for malignancy. The relative hazard of SI and malignancy comparing initiators of ADA and INF to ETN (the earliest biologic approved for RA) was estimated using covariate-adjusted Cox proportional hazards models. Analysis for malignancy was restricted to patients without a history of malignancy prior to cohort entry.

Results: Of 7,734 patients initiated an aTNF biologic with 13,296 PYs of observation. We identified 718 SIs and 179 malignancies during follow-up. IRs for SI were 48.2, 47.2, and 68.4 for ADA, ETN, and INF, respectively. Covariate-adjusted (age, gender, prior aTNF biologic use) hazard ratios (HR) for SI using all available follow-up were 0.97 (95% confidence interval [CI] 0.80–1.19) in ADA initiators and 1.34 (95% CI 1.13–1.58) in INF initiators. HRs for SI within the first 6 months of cohort entry were 1.10 (95% CI 0.78–1.56) in ADA initiators and 1.66 (95% CI 1.22–2.24) in INF initiators. IRs for malignancy were 15.5, 13.2, and 14.9 for ADA, ETN, and INF, respectively. Covariate-adjusted (age, gender, prior aTNF biologic use) HRs for malignancy using all follow-up time were 1.21 (95% CI 0.83–1.76) in ADA initiators and 1.10 (0.78–1.56) in INF initiators.

Conclusions: A higher SI rate was observed in RA patients initiating INF in comparison to ETN. Malignancy rates across aTNF biologic treatments were similar.

341. Occurrence of Osteonecrosis and Total Joint Replacement among Patients with Osteoarthritis

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Background: The incidence of osteonecrosis (ON) and total joint replacement (TJR) has not been well characterized among patients with osteoarthritis (OA).

Objectives: To calculate the incidence of ON and TJR among patients with OA, moderate-to-severe OA, and a general population cohort.

Methods: In this retrospective cohort study (data from 01 January 2002 through 30 May 2010) from a large US health insurance database, we identified patients with a diagnosis of OA and a general population cohort of similar size. Patients were followed for a diagnosis of ON and/or TJR. We identified a subset of patients with moderate-to -severe OA and followed them for the same outcomes. Incidence rates (IR) and 95% confidence intervals (95% CI) for ON and TJR were calculated. Cox proportional hazard models were used to estimate the relative hazard of ON and TJR.

Results: We identified 1,413,816 patients with OA, a subset of 781,424 patients with moderate-to-severe OA, and 1,185,602 persons in the general population cohort. In total, there were 7,391 cases of ON and 102,530 cases of TJR among the OA and general population cohorts with >2.5 million person-years of follow-up in each cohort. The IRs for ON outcomes ranged from 30.40 per 100,000 person-years for the general population (95% CI: 28.30–32.61) to 236.06 per 100,000 person-years for the OA cohort (95% CI: 230.43–241.80). The age-adjusted IRs for TJR in the OA cohort were 2,030.19 per 100,000 person-years (95% CI: 2,002.07–2,058.60), 2,519.85 per 100,000 person-years in the moderate-to-severe OA cohort (95% CI: 2,457.15–2,583.74), and 20.55 per 100,000 person-years in the general population cohort (95% CI: 19.23 – 21.93). For ON, the covariate adjusted hazard ratio (HR) comparing the OA cohort to the general population cohort was 4.95 (95% CI: 4.57–5.35). For TJR, the adjusted HR comparing the OA cohort to the general population cohort was 65.73 (95% CI: 61.78–69.93).

Conclusions: After adjustment for multiple confounding factors, the rate of ON in the OA cohort was approximately 5 times that of the general population and the rate of TJR in the OA cohort was approximately 66 times that of the general population cohort.

342. The Effect of Statin Use on Acute Kidney Injury Risk Following Coronary Artery Bypass Graft Surgery

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Background: Acute kidney injury (AKI) is a serious complication of cardiovascular surgery. Non-experimental studies suggest that pre-surgical statin use may reduce post-surgical AKI, but others have not found an association. Methodologic differences in study designs leave uncertainty regarding the magnitude or presence of the protective effect.

Objectives: We estimated the effect of pre-operative statin initiation on post-coronary artery bypass graft (CABG) AKI using a new epidemiologic approach more closely simulating a randomized controlled trial in a large CABG patient population.

Methods: We employed healthcare claims data from large, employer-based and Medicare insurance data. To minimize the healthy user bias we restricted our analysis to patients without a history of statin use. We identified 24,693 patients undergoing non-emergency CABG surgery who either newly initiated a statin within the 20 days prior to surgery or were unexposed for at least 200 days prior to CABG. AKI was identified in the 15 days following CABG from inpatient ICD-9-CM diagnosis codes. Multivariable Poisson regression was used to calculate adjusted risk ratios (RR) and 95% confidence intervals (CI). Analyses were repeated using propensity score methods adjusted for clinical and healthcare utilization variables.

Results: Post-CABG AKI developed in 3.7% of statin initiators and 6.2% of non-initiators. After adjustment for clinical characteristics and markers of disease management and healthcare utilization, we observed a protective effect of statin initiation on AKI (RR = 0.80, 95% CI 0.67, 0.96). This effect differed by age: ≥65 years, RR = 0.90 (95% CI: 0.71, 1.14); <65 years, RR = 0.69 (95% CI: 0.52, 0.91), although AKI was much more common in the older age group (8.1 vs. 3.9%).

Conclusions: Statin initiation immediately prior to CABG may modestly reduce the risk of post-operative AKI.

343. Statin Use and Risk of Atrial Fibrillation or Flutter: A Population-Based Case-Control Study

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Background: Statins are widely used as lipid-lowering agents, however some studies suggest that their pleiotropic effects may also reduce the risk of atrial fibrillation. Population-based evidence on this topic is still limited.

Objectives: To examine the association between statin use and atrial fibrillation or flutter.

Methods: We conducted a population-based case-control study using medical databases from Northern Denmark (population, 1.7 million) to identify 51,374 cases of a first hospital diagnosis of atrial fibrillation or flutter occurring between 1999 and 2010. For each case we selected 10 age-, sex-, and county-matched population controls. We collected data on statin prescriptions within 90 days (current users) or longer (former users) before the diagnosis date of atrial fibrillation or flutter, comorbidities, and other medications. We further stratified current and former users by duration of exposure, determined by counting the number of days between first and last day of prescription redemption before the diagnosis date of atrial fibrillation or flutter (short-term: <365 days, medium-term: 365–1,094 days, and long-term: ≥1,095 days). We defined people with no history of statin prescriptions as never users (reference). We used conditional logistic regression to compute odds ratios (ORs) and 95% confidence intervals (CIs), controlling for potential confounders and comorbidities.

Results: A total of 7,360 (14.3%) cases and 55,699 (10.8%) controls were current statin users; 2,928 (5.7%) cases and 23,185 (4.5%) controls were former users; 41,086 (80.0%) cases and 434,786 (84.6%) controls were never users. Among current users (adjusted OR: 0.96, 95% CI: 0.93–0.99), the effect of statins on preventing atrial fibrillation or flutter was related to duration of use: adjusted ORs decreased from 1.35 (95% CI: 1.28–1.42) for short-term users to 0.85 (95% CI: 0.81–0.89) for long-term users, compared with never users. For former users (adjusted OR: 0.94, 95% CI: 0.90–0.98), the ORs did not change varying the length of exposure.

Conclusions: Long-term current statin therapy may have a preventive effect against new-onset atrial fibrillation or flutter.

344. The Assessment of Statin-Associated Severe Muscle Toxicity in Japan- by Using Claims Database with Laboratory Information

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Background: To assess the drug safety efficiently, claims database with laboratory information are developed in many regions including Japan with a view to evaluate the drug-related risk.

Objectives: To evaluate the risk of severe muscle toxicity among statin users.

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Methods: This study was conducted within the cohort of 35,903 adult statin users (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin) by using a commercial database (Medical Data Vision Co., Ltd), which collected the information of medical service, prescription and lab test from 16 medical facilities during 2004–2010 in Japan. We determined whether the patients had any use of interacting drug (fibrates, triazoles, macrolides, macrolides, amiodarone, and ciclosporin) under statin therapy. The severe muscle toxicity is identified by muscle-related disorders diagnosis and/or creatine kinase (CK) concentration over ten times the upper limited of normal if there is no presence of disease-related condition accompanied to CK elevation like myocardial infarction, myocarditis, trauma and hypothyroidism within 3 days after muscle toxicity event. Incidence rates for sever muscle toxicity were determined per 1,000 person-years with 95% confidence intervals (CI) by Poisson regression with SAS version 9.3.

Results: A total of 18,036 patients contributed 42,193 person-years of statin therapy, 43 events were identified. Incidence of severe muscle toxicity in patients treated with statin ranged from 0.45 (95% CI, 0.19–1.08) with pravastatin to 1.73 (95% CI, 1.04–2.87) with rosuvastatin per 1,000 person-years. Using atorvastatin users as reference, there were no significant differences among statins with respect to incidence of severe muscle toxicity. Of 2,430 (13.5%) of patients treated with statin have received interacting drug during follow-up period. As result of few events with low number of person-years of receiving interacting drug, our finding showed the wide 95% CI around the incidence rate point estimate.

Conclusions: Our finding suggested that the use of statin is generally well tolerate and safe, however, the risk of sever muscle toxicity related to interacting drug use needed further explored.

345. Cardiovascular Risk of Olmesartan (Olm) Compared with Other Angiotensin-II Receptor Blockers (ARBs)

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Background: The randomized trial, ROADMAP, reported an increased risk of acute myocardial infarction (AMI) and cardiac death in Olm-treated diabetic patients with ≥1 additional cardiovascular (CV) risk factor vs. placebo.

Objectives: To test if risk of AMI, stroke, or death is increased in patients treated with Olm compared with other-ARBs, in all users and pre-specified subgroups with and without treated diabetes (DM) and/or ischemic heart disease (IHD).

Methods: Retrospective new-user cohorts of patients initiating ARB therapy from 2007 to 2010.

Setting: Community-dwelling, Medicare beneficiaries age ≥65 years with at least 12 months prior enrollment in Parts A, B, and D.

Exposures: Olm vs. pooled other-ARBs.

Outcomes: Hospitalized AMI, stroke, and death.

Statistics: Multivariable Cox proportional hazards regression, with pre-specified analyses of effect modification by DM and IHD.

Results: Cohorts included 158,054 Olm- and 724,673 other-ARB-treated patients, 96% with hypertension (HTN), with combined follow-up of 314,674 person-years, during which there were 3,722 AMIs, 3,002 strokes, and 2,668 deaths. Adjusted hazard ratios (HR) (95% CI) with other-ARBs as reference were AMI: 0.92 (0.84–1.01); stroke: 1.01 (0.91–1.11); death: 0.83 (0.74–0.93). In subgroup without IHD, AMI: 0.86 (0.76–0.98); in DM subgroup (to compare with ROADMAP), AMI: 0.95 (0.81–1.13); stroke: 1.01 (0.83–1.24); death 0.94 (0.76–1.16). In post hoc analyses, including adjustment for leading causes of death in US elderly and potential sources of channeling, the HR for death was unchanged from main results; HR for AMI with Olm was reduced in patients with HTN and no other labeled indication for ARB use.

Conclusions: In patients with treated DM, CV and mortality risks were not increased by Olm vs. use of other-ARBs. Unexpectedly, risk of death was reduced in Olm-treated patients and risk of AMI was reduced in Olm-treated patients with HTN and no other indication for ARB use. Confounding by measured risk factors did not explain these findings and evidence of channeling was not found. Randomized trials would be needed to determine if Olm has cardioprotective effects compared with other-ARBs.

346. Angioedema Events and Use of Drugs That Act on the Renin-Angiotensin-Aldosterone System (RAAS)

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Background: Angiotensin converting enzyme inhibitors (ACEIs) have been linked to an increased risk of angioe-

dema, but risk for other drugs acting on RAAS is not well characterized.

Objectives: To assess the risk of angioedema in users of ACEIs, angiotensin receptor blockers (ARBs), and the direct renin inhibitor, aliskiren.

Methods: We identified ACEI, ARB, and aliskiren initiators in 2001–2010 from 17 Data Partner sites in Mini-Sentinel. Eligible individuals were free from previous dispensing of any study drugs and diagnosis of angioedema during 183-days preceding first dispensing of a study drug. They were followed from treatment initiation to earliest occurrence of angioedema (identified by an inpatient, emergency department, or outpatient ICD-9-CM diagnosis code 995.1; PPV: 90–95% in previous studies), 365 days of follow-up, initiation of another study drug, treatment cessation, death, disenrollment, or 12/31/2010. Risk of angioedema for each drug class was compared separately with a common referent group not thought to be associated with angioedema, ß-blockers, using the case-centered logistic regression approach (equivalent to a Cox model stratified by propensity score [PS] quintile and site). The PS was estimated separately for each pair at each site using age, sex, prior diagnosis of allergic reactions, diabetes, heart failure, and ischemic heart disease, and prescription NSAID use as predictors.

Results: There were 3,301 angioedema cases in 1,845,138 ACEI initiators, 288 cases in 467,313 ARB initiators, 7 cases in 4,867 aliskiren initiators, and 915 cases in 1,592,278 ß-blocker initiators. Compared to ß-blockers, the hazard ratio (HR) adjusted for site was 2.77 (95% CI: 2.57, 2.98) for ACEIs, 1.11 (0.97, 1.28) for ARBs, and 2.75 (1.30, 5.81) for aliskiren. The PS-adjusted HR was 3.04 (2.81, 3.27) for ACEIs, 1.16 (1.00, 1.34) for ARBs, and 2.85 (1.34, 6.04) for aliskiren.

Conclusions: ACEIs were associated with a threefold higher risk of angioedema vs. ß-blockers. Aliskiren may also increase the risk of angioedema compared to ß-blockers, although the number of events was small. Risk of angioedema was lower for ARBs than with ACEIs and aliskiren.

347. Risk of Acute Renal Failure Likely Due to Concurrent Use of ACE-Inhibitors, Angiotensin Receptors Blockers, Diuretics and Anti-Inflammatory Drugs

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Background: The terms "double" and "triple whammy" have been coined to define the renal adverse effects likely due to the combination of one or two medications among ACE-inhibitors (ACEI), angiotensin receptor blockers (ARBs) and diuretics, with non-steroidal anti-inflammatory drugs (NSAIDs).

Objectives: To assess whether double and triple whammy were associated with a greater risk of acute renal failure (ARF).

Methods: We conducted a nested case-control analysis within a cohort of 1,369,967 users of antihypertensive drugs using the United Kingdom's General Practice Research Database (GPRD). All cases of ARF occurring during follow-up (index date) were identified on the basis of Read codes. Up to 10 controls were randomly selected and matched to each case on year of birth, sex, calendar year of cohort entry, and duration of follow-up. Exposure to double or triple whammy was defined as the overlap in prescription coverage between NSAIDs and ACEI/ARBs and/or diuretics. Current use was defined when the exposure prescription coverage overlapped the index date or ended within 90 days of index date. Conditional logistic regression was used to estimate the adjusted rate ratios (RRs) along with 95% confidence intervals (CI) of ARF associated with double and triple whammy.

Results: Within the cohort of antihypertensive users, a total of 6,412 cases of ARF were identified during follow-up (incidence rate = 8/10,000 per year). Current use of a double whammy with NSAIDs was associated with an increased rate of ARF (RR: 1.26, 95% CI: 1.11–1.43) for diuretics, and for ACEI/ARBs (RR: 1.11, 95% CI: 0.96–1.28). An increased risk was also observed for triple whammy (RR: 1.22, 95% CI: 1.12–1.33). Furthermore, for both double and triple whammy, the risk was highest during the first 30 days after treatment initiation.

Conclusions: Double and triple whammy from the combination of anti-hypertensives and NSAIDs can increase the risk of ARF, particularly at the start of treatment. Although antihypertensive medications have well-known benefits on cardiovascular events, some vigilance may be warranted when they are concurrently taken with NSAIDs.

348. International Comparison of the Utilisation of Anti-Diabetic Medicines

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Background: There is no study comparing the utilisation of anti-diabetic medicines between Australia and European countries.

Objectives: To examine the use of anti-diabetic medicines between Australia and eight European countries from 2001 to 2010 and investigate possible factors influencing drug use patterns.

Methods: A longitudinal, cross-national drug utilisation study on anti-diabetic medicines was conducted. The anti-

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diabetic medicines studied were metformin, sulphonylureas, insulin, glitazones, acarbose, gliptins, exenatide and oral hypoglycaemic combination products. Data were collected from nine countries:

Australia, Denmark, England, Finland, France, Iceland, the Netherlands, Norway and Sweden. Data were expressed in DDD/1,000 inhabitants/day. Possible factors influencing the trends of usage such as diabetes prevalence, pharmaceutical reimbursement policies, response to safety studies and timing of safety warnings were identified through a literature search.

Results: Usage of total anti-diabetic medicines increased from 2001 to 2010 across all countries. Finland reported the highest usage of total anti-diabetic medicines. This could be possibly explained by high prevalence of both type 1 and type 2 diabetes in Finland. The use of metformin increased in all countries, which was in concordance with the current treatment guidelines. The use of rosiglitazone decreased in all countries after 2007 following the concerns of increased risk of cardiovascular events. Different patterns of pioglitazone usage were observed across countries, likely to be in response to different interpretations of the benefit to risk ratio of this drug. The use of newer anti-diabetic medicines such as gliptins, exenatide and oral hypoglycaemic combination products increased in all countries and represented for up to 5% of total anti-diabetic medicines in 2010.

Conclusions: We found an overall increase in the utilisation of anti-diabetic medicines in all countries examined. The patterns of use of anti-diabetic medicines were in concordance with the current treatment guidelines. Diabetes prevalence, pharmaceutical reimbursement policies, timing of safety warnings and pharmaceutical promotion can all influence drug use.

349. The Impact of a National Program on Judicious Use of Antidiabetic Medicines

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Background: Australia has about 1 million (4.4%) people diagnosed with diabetes, and a similar number may be undiagnosed. There are multiple gaps between evidence and practice in therapeutic management for diabetes. NPS has made a significant effort to promote evidence-based diabetes management over the last decade.

Objectives: To assess impact of the national program on quality prescribing for diabetes management.

Methods: Retrospective study of the association between general practitioner (GP) participation in the program and prescribing rates for insulin, glitazones and metformin, as recorded by the Pharmaceutical Benefits Scheme (PBS).

Interventions: Interventions included educational visits, case studies, audits, workshops and group discussions. The 2008/9 program key messages included: initiate insulin early; ensure metformin is part of ongoing therapy and the use of glitazones does not delay progression to insulin; and review use of glitazones in heart failure and ischaemic heart disease.

Outcome measures: Differences in prescribing rates per 1000 consultations for antidiabetics with and without NPS intervention.

Statistical analysis: Interrupted time series modelling was used to assess the association between GP participation in NPS programs and the prescribing rate, controlling for underlying secular trends, seasonality, autocorrelation, FDA warnings and policy changes.

Results: We found significant associations between GP participation and changes in prescribing rates for insulin and glitazones. GP participation (9,496) in the diabetes program led to a 7% relative increase ($p < 0.001$) in prescribing for insulin per 1000 GP consultations in 2008 and a further 11% increase in 2009. GP participation also led to a 13% relative decrease in glitazone prescriptions per 1,000 GP consultations in 2008 and a further 16% decrease in 2009. While the rate of metfomin prescribing increased over this period, the program was not found to be associated with this increase.

Conclusions: Multi-pronged interventions in general practice can significantly impact the use of antidiabetics at a national level. A new diabetes program, which is in line with updated guidelines, is currently under development.

350. Validation of Diabetic Retinopathy and Maculopathy Diagnoses Recorded in a United Kingdom Primary Care Database

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Background: Validation of diagnosis codes is a highly recommended step in order to offer reliable epidemiological measures in research performed in automated healthcare databases.

Objectives: To describe the validity of recorded diabetic retinopathy (DR) and maculopathy (DMP) diagnoses, including macular oedema (DMO) in The Health Improvement Network (THIN) UK primary care database.

Methods: In two independent computer searches, we identified 20,838 diabetics aged 1–84 years with a first DR computer Read code entry in 2000–2008, and 4,064 with a first DMP entry. A two-step strategy was used to validate both outcomes: (1) for all DMP patients and a random sample of 500 DR patients a manual review of computerized patient profiles was conducted. Profiles included free-

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text comments from primary care practitioners' (PCPs) with referral information and test results. We classified subjects into probable case, possible case, and non-case according to the plausibility of the diagnosis. (2) for a random sample of 200 subjects with DR and 200 subjects with DMP (including 36 DMO) questionnaires and additional medical records information were requested to PCPs and reviewed. Confirmation of diagnosis by PCP was considered the gold standard.

Results: After revision of the random sampled patient profiles with free-text comments, we categorized 418 DR cases and 3,676 DMP cases as probable/possible (including 711 DMO). After review of the information received from PCPs, probable/possible cases of DR and DMP were respectively confirmed in 87.3% and 87.2% of instances. Confirmation rate for DMO was 90.3%. The confirmation rates, once applied to the whole population of automatically computer-detected patients, translated into a weighted confirmation rate of 78.0% for DR codes, 79.0% for DMP codes, and 86% for DMO codes.

Conclusions: Read codes for DR, DMP, and DMO showed a moderate accuracy in identifying incident cases of these ophthalmologic complications. The validity further improved when incorporating PCPs' text comments to the patient's profile.

351. Aspirin and the Risk of All-Cause Mortality in New Users of Oral Antidiabetes Drugs

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Background: Use of aspirin is widely recommended in diabetes clinical guidelines yet its effect on the risk of mortality for individuals with type 2 diabetes remains largely unknown.

Objectives: To evaluate the association between aspirin use and mortality among individuals who initiated an oral antidiabetes drug treatment.

Methods: Using Quebec administrative databases, we conducted a case-control study nested in a cohort of 99,670 individuals aged ≥18 years, newly treated with an antidiabetes drug between 2000-01-01 and 2007-12-31, and followed up until 2008-12-31. Individuals had not used aspirin, antiplatelet or anticoagulant drugs and had no gastro-intestinal bleeding in the year before cohort entry. Cases were individuals who died during follow-up. For each case, five controls were matched for age, year of cohort entry, sex and cardiovascular disease using incidence density sampling. Exposure to aspirin was defined as current, past or no use. Current users were those whose last aspirin prescription overlapped with the index date (i.e., end of days supply plus a grace period of 10 days). Using paired multivariate conditional logistic regression, we calculated adjusted odds ratios (AOR) of all-cause mortality. To test the sensitivity of the length of the grace period in defining current users, we repeated the analysis using: (1) no grace period; (2) a grace period equalled to the number of days supply.

Results: A total of 8907 patients (8.9%) died. Compared to non-users of aspirin both current (AOR: 0.80; 95% CI: 0.76–0.87) and past (0.64; 0.57–0.73) users had a reduced risk of mortality. The results did not differ in the sensitivity analyses.

Conclusions: In this population of individuals newly treated with antidiabetes drugs, current or past use of aspirin was associated with reduced all-cause mortality. This result suggests that aspirin might have a protective effect although healthy-user bias cannot be ruled out.

352. Statin Initiation in Elderly Patients Using Antidiabetes Drugs

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Background: The underprescription of statins is frequent in the elderly. However, the benefit of statins is well demonstrated for primary and secondary prevention of cardio-vascular diseases in elderly diabetic patients.

Objectives: To estimate the rate of statin initiation among elderly patients undertaking insulin or oral antidiabetes drug (AD) treatment and to identify factors associated with this initiation.

Methods: Using the Quebec Health Insurance Board databases, we conducted a population-based cohort study of individuals aged ≥65 years who were newly dispensed an AD between 2000-01-01 and 2008-12-31. Those using statin in the year before were excluded. The rate of statin initiation was calculated and factors associated with statin initiation were identified with multivariable Cox regression.

Results: In this cohort of 56,687 AD new users, the incidence rate of statin initiation was 19.10 cases per 100 patient-years. Patients who were less likely to initiate statin had initially received sulfonylurea alone (Adjusted hazard ratio: 0.83; 95%CI: 0.80–0.86) or insulin alone (0.64; 0.56–0.72) vs. metformin alone, were aged ≥76 (0.51; 0.49–0.53) vs. 65–69 years, or, in the year prior to the AD initiation, had received three to five (0.89; 0.86–0.91) or >6 (0.76; 0.74–0.79) different medications, taken antihypertensive treatment alone (0.92; 0.89–0.95), or antidepressants (0.93; 0.89–0.97). In contrast, patients who were

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more likely to initiate statin had suffered from ≥2 cardiovascular diseases in the year prior to initiating AD (1.72; 1.61–1.85). The rate of statin initiation increased significantly from 2000 to 2008.

Conclusions: Among elderly patients not on statins before the beginning of their AD treatment, the initiation rate of statins is low. Several factors are associated with this initiation and could be considered in future interventions aiming to improve the cardiovascular protection of those patients.

353. Antipsychotics and the Risk of Type 2 Diabetes in Children and Youth

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Background: Considerable evidence suggests that some atypical antipsychotics increase the risk of type 2 diabetes in adults. Marked increases in antipsychotic drug prescribing in children/youth has heightened concerns over the possible link between antipsychotic use and increased risk of type 2 diabetes in this population.

Objectives: To assess whether the risk of newly diagnosed type 2 diabetes was increased with use of antipsychotics in a large cohort of children/youth, aged 6–24 years.

Methods: We conducted a retrospective cohort study using computerized files of the Tennessee Medicaid program (1996–2007), augmented with linkage to a statewide hospital discharge database. Cohort antipsychotic users initiated antipsychotic therapy within 90 prior to the beginning of follow-up, with no other antipsychotic drug use in the 365 days preceding that fill. Controls were selected from analogously defined recent initiators of other psychotropic drugs, frequency matched with antipsychotic users according to propensity score. Newly diagnosed cases of diabetes were identified with a computer definition that was validated in a sample of the study cohort.

Results: Antipsychotic users had a three-fold increased risk for type 2 diabetes (HR 3.03, 95% CI 1.73–5.32) that was apparent within the first year of follow-up, and increased with cumulative antipsychotic drug dose. For children (< 18 years old), antipsychotic users had more than a three-fold increased risk of type 2 diabetes (HR 3.14, 95% CI 1.50–6.56), which also increased with increasing cumulative doses. Antipsychotic users had no significantly increased risk for type 1 diabetes.

Conclusions: In the study cohort of children/youth aged 6–24 years, antipsychotic users had a three-fold greater risk of newly diagnosed type 2 diabetes than did propensity-score matched control medication users. The excess risk occurred within the first year of antipsychotic use, increased with increasing cumulative dose, and was present for children < 18 years of age.

354. Validity of Diagnostic Codes and Liver-Related Laboratory Abnormalities To Identify Acute Liver Failure among Kaiser Permanente Patients with Diagnoses of Drug-Induced Hepatitis

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Background: Accurate methods to electronically identify acute liver failure (ALF) from drug-induced hepatitis would facilitate evaluation of hepatic safety of medications in real-world settings and post-marketing surveillance by regulatory agencies.

Objectives: To determine the ability of diagnostic codes and liver-related laboratory abnormalities to identify ALF among Kaiser Permanente Northern California (KPNC) members with drug-induced hepatitis diagnoses.

Methods: We performed a cross-sectional study in KPNC (2004–2010) who had: (1) ICD9 diagnosis of drug-induced hepatitis (toxic hepatitis [573.3] or drug-induced liver disorder [573.8]); (2) inpatient ICD9 diagnosis suggesting ALF (acute hepatic necrosis [570], hepatic coma [572.2], hepatorenal syndrome [572.4], other liver disease sequelae [572.8], liver transplant [V42.7]) and laboratory results indicating liver injury (total bilirubin ≥5.0 gm/dL and INR ≥1.5 [off warfarin]) within 182 days of the drug-induced hepatitis diagnosis; and (3) no chronic liver disease diagnosed prior to the drug-induced hepatitis diagnosis. Inpatient records were reviewed by hepatologists, who adjudicated whether these were ALF events. Positive predictive values (PPVs) of combinations of diagnostic codes and lab results for confirmed ALF were determined.

Results: Among 110 patients with drug-induced hepatitis who were hospitalized with an ALF diagnosis and liver injury, 30 were confirmed to have ALF (PPV, 27%; 95% CI, 19–36%). Requiring at least two inpatient ALF diagnoses with lab results of liver injury increased the PPV for

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confirmed events (PPV, 34%; 95% CI, 20–49%), and the highest PPVs were for the combination of acute hepatic necrosis plus either hepatorenal syndrome (PPV, 67%; 95% CI, 30–93%) or hepatic coma (PPV, 59%; 95% CI, 33–82%).

Conclusions: Among patients with diagnoses of drug-induced hepatitis, inpatient diagnoses of ALF and laboratory results indicating liver injury had low PPV for confirmed ALF events. Until a validated algorithm for ALF is developed, studies evaluating this endpoint should confirm ALF with review of medical records.

355. Validity of Administrative Data To Identify Off-Label Use of Second Generation Antipsychotics

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Background: Drug utilization studies consistently find that nearly two-thirds of second generation antipsychotic (SGA) use is for off-label conditions. Prevalent off-label prescribing contributes to rising costs for the US Medicaid program. The accuracy Medicaid administrative data for identifying approved diagnoses in patients using SGAs is unclear.

Objectives: The objective of this study was to determine the accuracy of administrative data to identify off-label prescribing for SGAs.

Methods: We used a cross-sectional approach to assess the agreement between Medicaid billing data from the State of Oregon and diagnosis information obtained from a local health system's electronic health record (EHR) in the year 2009. Inclusion criteria were continuous Medicaid enrollment, at least one prescription for a SGA, and two or more documented encounters within the health system EHR during the study year. ICD9 billing codes were used to identify patients with major FDA-approved conditions: schizophrenia, bipolar disorder, and depression. Concordance with diagnoses listed in the EHR was evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) overall and within subgroups characterized by SGA utilization.

Results: Of the 822 study subjects included, 245 (29.8%) had an EHR documented diagnosis of schizophrenia, bipolar disorder, or depression. For schizophrenia, the sensitivity, specificity, PPV and NPV of administrative data was 79.1% (95% CI 67.4–88.1%), 89.5% (95% CI 87.1–91.6%), 40.2% (95% CI 31.7–49%), and 98% (95% CI 96.6–98.9%) respectively. The sensitivity, specificity, PPV, and NPV for the diagnosis of bipolar disorder was 84.7% (95% CI 75.3–91.6%), 79.2% (76.1–82.1%), 32% (95% CI 26–38.5%), and 97.8% (95% CI 96.3–98.8%) respectively. Claims data showed similar discrimination for the diagnosis of depression as well in subgroups restricted by SGA chronic use or estimated daily dose.

Conclusions: The PPV in this population of SGA users was relatively poor (41%). However, the high NPV suggests claims data may be helpful for identifying which SGA users do not have a FDA-approved condition.

356. Validation of ICD9 Coding as Reported in Administrative Data – Results from a Review of Patient Medical Records

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Background: There is a need to evaluate the accuracy of ICD9-based coding systems in administrative databases used for observational studies.

Objectives: To evaluate the accuracy of coding data in an administrative database compared to patient medical record.

Methods: Patients receiving certain carbapenems during an inpatient hospitalization between January 1, 2006 and December 31, 2010 were identified from a hospital administrative database. An algorithm of ICD9 diagnosis, procedure codes, and CPT4 procedure codes was developed to identify patients with complicated Urinary Tract Infections (cUTI) or complicated Intra-abdominal Infections (cIAI). A random sample of these patients was selected for review of their medical records. Abstractors recorded the presence or absence of 121 individual codes as well as patient demographic (e.g., age, gender, admission and discharge dates) and treatment variables (DORIPENEM, IMIPENEM,) for the index hospitalization. An infection control physician reviewed the abstracted data and assessed agreement between the administrative database and charts. Positive (PPV) and Negative Predictive Values (NPV) as well as sensitivity and specificity were calculated for each individual code as well as cUTI and cIAI as defined by the algorithm and treatment with either DORIPENEM or IMIPENEM.

Results: Two hundred two patient medical records were reviewed to assess 121 ICD9 and CPT codes, four patient demographic variables, and four treatment related variables for each patient (26,058 observations). Overall comparisons of ICD9 data to the abstracted data for the cUTI algorithm were 98.2% PPV, 16.7% NPV, 84.5% sensitivity, and 33.3% specificity; for the cIAI algorithm the results were 72.2% PPV, 100.0% NPV, 100.0% sensitivity, and 94.3% specificity. Receipt of DORIPENEM results were 97.6%, 98.7%, 99.2%, and 96.1% and for

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receipt of IMIPENEM 93.3%, 99.2%, 98.6%, and 96.2% for PPV, NPV, sensitivity, and specificity respectively.

Conclusions: The PPV and NPV for the algorithm to identify cUTI and cIAI of administrative data was high. Review of patient medical records by an abstractor was comparable to data obtained from a hospital administrative database.

357. Performance and Validity of Record Linkage without Unique Personal Identifiers

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Background: Linking clinical/device registries with administrative databases can enhance the utility of the databases for comparative effectiveness research. In the absence of unique personal identifiers(UPIs) such as social security numbers (SSNs), records can be linked using multiple non-unique personal identifiers(nUPIs) such as date of birth (DOB), sex, admission date (AdmD) and provider IDs (pIDs).

Objectives: To assess the performance and validity of record linkage method without using UPIs.

Methods: Using CMS implantable cardioverter defibrillator (ICD) registry and the Medicare inpatient files that contain SSNs, we tested four rules (R1–R4) using different combinations of nUPIs to link records from 2005 to 2008. We estimated linkage rate(LR) as the number of unique linkages produced by each rule divided by the number of total registry records. We expected ≤80% will link since the Medicare files do not include the non-fee-for-service beneficiaries or veterans who are part of the registry. Sensitivity (Sens), specificity (Spec) and positive predictive value (PPV) were derived in comparison to a gold-standard (GS) linkage based on SSN, AdmD and pID.

Results: We identified 136,511 unique linkages between the registry and Medicare files using the GS (SSN + AdmD + pID, LR 58%). R1, which required a match on all nUPIs (DOB + sex + AdmD + pID), had the highest LR (55.2%), closely followed by 55.0% for the rule with imperfect provider information (R2: DOB + sex + AdmD + provider state). Rules using fewer nUPIs to link records had much lower LRs (R4:DOB + sex + pID = 19%, R3:DOB + sex + AdmD = 0%). The rule without provider information (R3) produced only five unique linkages. R1 had the highest validity (Sens 95%, Spec 98%, PPV 98%) compared to the GS, followed by R2 (Sens 89%, Spec 91%, PPV 93%), R4 (Sens 19%, Spec 82%, PPV 57%) and R3 (Sens 0%, Spec 100%, PPV 0%).

Conclusions: The linkage rules using multiple non-unique personal identifiers produced specific linkages, but lack sensitivity due to missing value or errors in linkage variables. The GS linkage might have incomplete sensitivity possibly due to errors in SSNs. In the absence of a unique personal identifier, provider information appears useful for successful linkage.

358. Validation of Congenital Malformation Diagnostic Codes Recorded in Québec Administrative Databases

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Background: The validity of the diagnostic information recorded in health administrative databases is often questionable, because diagnoses are primarily coded for billing and not for research purposes.

Objectives: To examine the validity of the diagnostic codes related to congenital malformations recorded in the Québec administrative databases among babies born to women with and without asthma.

Methods: Using a large cohort of pregnancies from asthmatic and non-asthmatic women and their babies that was reconstructed between 1990 and 2002 from the linkage of three Québec databases (RAMQ, MED-ECHO, ISQ), we selected babies with and without diagnoses of congenital malformations. The diagnosis of congenital malformations derived from the RAMQ and MED-ECHO databases was compared to the diagnosis written in the baby's medical chart ("gold standard"). We estimated the predictive positive value (PPV) and the predictive negative value (PNV) for any congenital malformation identified from the databases and corresponding 95% confidence intervals (CI). We also estimated the PPV for major congenital malformations and for several groups of congenital malformations.

Results: Selected babies from asthmatic women included 496 with at least one congenital malformation and 256 without a congenital malformation recorded in the databases. The corresponding figures for babies of non-asthmatic women were 404 and 138, respectively. The PPV of having any or a major congenital malformation were 82.7% (95% CI: 80.0–85.4) and 79.2% (95% CI: 76.3–82.1), respectively, in the asthma group, while they were 82.2% (95% CI: 79.0–85.4) and 78.4% (95% CI: 74.9–81.8), respectively, in the non-asthma group. In both groups, high PPVs (>80%) were found for several specific congenital malformations including cardiac, clefts, climbs, digestive, urinary and genital malformations. The PNV for any congenital malformation was 91.0% (95% CI:

89.0–93.1) in the asthma group and 94.2% (95% CI: 92.2–96.2) in the non-asthma group.

Conclusions: Québec databases are a valid tool for epidemiological research on congenital malformations, with no differences observed between babies born to women with or without asthma.

359. Estimating Disease Progression in Metastatic Cancer Patients Using Dispensing Data: A Validation Study

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Background: Increasingly, clinical trials establishing the efficacy of cancer treatments use surrogate endpoints such as time to disease progression over traditional endpoints such as overall survival. The availability of large population-based health administrative data sets has enhanced significantly the evaluation of cancer drug performance in routine clinical care. However, estimating surrogate endpoints in these data sets is challenging due to the absence of detailed clinical information.

Objectives: To derive and validate a proxy for disease progression in metastatic breast, lung and colorectal cancer patients using prescribing and dispensing data.

Methods: Our derivation and validation populations are all enrollees in the EoCC study who had consented to medical record review (including chemotherapy charts and imaging records) and linkage to administrative health data (including pharmaceutical claims). We derived the proxy decision rules using the prescription histories extracted from the chemotherapy charts of 41 patients. The proxy is based on changes in drug treatment (cytotoxic and targeted therapies) and distinguishing between changes due to progression, toxicity and standard care. We validated the proxy using the prescription histories of another cohort of 71 metastatic cancer patients. The proxy is validated against our gold standard: disease progression as recorded in patient medical records. We used GEE to calculate sensitivity and specificity to account for within patient clustering (at least one progression is observed per patient).

Results: The sensitivity and specificity of our proxy in prescribing data was 90.0% (95%CI: 73.7–96.7%) and specificity is 88.2% (95%CI: 77.0–94.4%).

Conclusions: We have developed a robust proxy for disease progression in prescribing data and we are currently applying and validating the proxy using the dispensing history of another cohort of 93 metastatic cancer patients. The proxy shows promise for applicability in health administrative data to infer disease progression in real-world outcome studies.

360. Long-Term Active Surveillance Study for Oral Contraceptives (LASS): Final Results on Cardiovascular Safety

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Background: Progestins used in oral contraceptives (OCs) have substantially distinct pharmacological profiles. The progestin drospirenone (DRSP) has antimineralocorticoid properties which potentially could have beneficial as well as unfavorable effects on cardiovascular outcomes.

Objectives: To assess the risk of venous (VTE) and arterial thromboembolic events (ATE) associated with oral contraceptives containing DRSP, levonorgestrel (LNG) and other progestogens (OP).

Methods: Controlled, prospective, non-interventional cohort study of 59,510 new users of new and established OCs that investigates the safety of OC use under routine medical conditions. Study participants were recruited via a network of gynecologists in seven European countries. Follow-up for up to 10 years. Baseline and follow-up information were collected via self-administered questionnaires. A multifaceted 4-level follow-up procedure ensured a low loss to follow-up rate (2.9%). The analysis is based on Cox regression models. VTE hazard ratios (HRs) were adjusted for age, BMI, duration of current use and family history of VTE; ATE HRs were adjusted for age, BMI, smoking, family history of fatal ATE and hypertension.

Results: The analysis is based on 318,784 women-years of observation, 306 VTE and 84 ATE. The VTE incidence rates for DRSP, LNG and OP were 10.7 (95% CI: 8.1–13.9), 9.2 (95% CI: 6.9–12.0), and 13.6 VTE/10,000 WY (95% CI: 11.4–16.0). The corresponding ATE incidence rates were 1.3 (95% CI: 0.5–2.8), 3.8 (95% CI: 2.4–5.8) and 3.2 ATE/10,000 WY (95% CI: 2.2–4.5). The adjusted VTE hazard ratios (HRs) for DRSP vs. LNG and DRSP vs. OP were 1.1 (95% CI: 0.8–1.7) and 0.7 (95% CI: 0.5–1.0), respectively. The corresponding HRs for ATE were 0.4 (95% CI: 0.2–0.9) and 0.4 (95% CI: 0.2–0.9).

Conclusions: These results suggest that the risk of VTE for DRSP-containing OCs is not higher than the VTE risk associated with the use of LNG-containing OCs or OP, while the ATE risk appears to be lower compared with other OCs.

361. VTE Risk in Users of Combined Oral Contraceptives: Impact of a 24-Day Regimen Containing Drospirenone

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Background: Fluctuations of serum hormone levels influence the risk of venous thromboembolism (VTE). Shortening of the pill-free interval in combination with a

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progestin with a long half-life leads to less fluctuation of hormone levels and might have an impact on the incidence of VTE associated with oral contraceptives.

Objectives: To assess the risk of VTE associated with a 24-day drospirenone contraceptive regimen (DRSP 24d). This is compared to established OCs in a study population that is representative of actual OC users.

Methods: The INternational Active Surveillance Study of women taking Oral Contraceptives (INAS-OC) is a prospective, controlled, non-interventional cohort study carried out in the US and 6 European countries with three cohorts: DRSP 24d, DRSP 21d, Other OCs. New users of an OC (starters, restarters or switchers) are recruited by a network of prescribing physicians and contribute follow-up information for 3–5 years after study entry. All self-reported clinical outcomes of interest are validated by health care professionals. Main clinical outcomes of interest are venous thromboembolisms (deep venous thrombosis, pulmonary embolism) and arterial thromboembolisms (acute myocardial infarction and cerebrovascular accidents). Data analysis is based on life-table methods. All analyses make allowance for confounding, using multivariate techniques such as Cox regression models.

Results: A total of 85,260 study participants were recruited. The analysis is based on 166,000 women-years (WY) of observation and 122,000 WY of OC exposure. Overall, 110 VTEs have occurred in OC users (DRSP 24d: 17, DRSP 21d: 9, Other OCs 84). The overall VTE incidence is 9.0/10,000 WY (95% CI: 7.4–10.9). For the three cohorts the VTE incidence is 7.6 (DRSP 24d), 6.8 (DRSP 21d) and 9.7 (Other OCs), respectively. The crude hazard ratio (HR) for DRSP 24d vs. Other OCs is 0.8 (95% CI: 0.4–1.3). Adjustment for age, BMI, duration of current OC use and family history of VTE leads to an adjusted HR of 0.9 (95% CI: 0.5–1.5).

Conclusions: The results suggest that the VTE risk of DRSP 24d users is similar to users of other OCs in a study population that is representative of actual OC users.

362. Patterns of antihypertensive medication use in medicaid-eligible pregnant women

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Background: Hypertensive disorders occur in approximately 6–8% of all pregnancies and are a significant source of maternal and fetal morbidity. While methyldopa and labetalol are generally considered in guidelines as the first line/preferred agents for the treatment of hypertension in pregnancy, experts suggest that other antihypertensive medications (AHM) can also be safely used. Little is known about the range of agents routinely used in practice.

Objectives: To describe patterns of AHM use during pregnancy in a cohort of Medicaid-eligible women in the US.

Methods: We used Medicaid claims from 2000 to 2007 to identify completed pregnancies. We estimated the date of last menstrual period (LMP) based on the delivery date, adjusted for diagnostic codes for pre-term delivery. We included women who were (1) Medicaid beneficiaries from at least 3–months pre-LMP to 1 month post-delivery, and (2) were successfully linked to infant records. Maternal exposure to AHM was derived from Medicaid pharmacy claims files.

Results: We identified 1,106,757 Medicaid patients in our cohort of whom 48,452 (4.4%) were exposed to AHMs during pregnancy. The prevalence of antihypertensive use increased from 3.5% to 4.9% during the study period. AHM users were older than non-users, more likely to be Caucasian or African-American, and more likely to have comorbid diabetes and/or renal disease. Overall, 1.9% of pregnant women were exposed during the 1st trimester, 1.7% during the second trimester, and 3.2% during the third trimester. The range of AHMs to which patients were exposed was highly heterogeneous – 63% of exposures in the first trimester, 43% in the second trimester, and 60% in the third trimester were to agents other than methyldopa or labetalol. ACE inhibitor exposure, which is clearly contraindicated in late pregnancy, occurred in 928 (4.9%) AHM users in the second trimester and 383 (1.1%) in the third trimester.

Conclusions: Antihypertensive use during pregnancy is common and increasing. The wide range of agents used during pregnancy includes medications considered contraindicated during pregnancy. Data on the comparative safety and efficacy of specific antihypertensives in pregnant women are urgently needed.

363. Drospirenone vs. Other Progestin-Based Combined Oral Contraceptives and the Risk of Incident Ulcerative Colitis: A Comparative Safety Study

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Background: Combined oral contraceptive (COC) use has been associated with risk of ulcerative colitis (UC).

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Epidemiologic studies on COCs and UC risk are limited.

Objectives: To evaluate comparative safety of alternative COCs on the occurrence of UC amongst women aged 18–46 years.

Methods: The IMS LifeLink Database is comprised of US managed care health plans. We identified a retrospective cohort of women who were initiators of progestin-based COCs containing ethinyl-estradiol (desogestrel, drospirenone, levonorgestrel, norethindrone, norethindrone acetate, norgestimate, and norgestrel) from January 1, 1997, through December 31, 2009. The index date was the first prescription of a study COC after one full year of enrolment. We excluded women who had claim-based diagnosis of Irritable Bowel Disease during the prior year. A confirmed case of UC required a minimum of five separate inpatient and/or outpatient claims for UC, a previously validated method. We analyzed the risk of UC comparing drospirenone use to other COCs using Cox proportional hazards models adjusting for smoking, NSAID use, PCOS, acne, PMDD, diabetes, hypertension, and hyperlipidemia.

Results: Among 1,625,262 COC-initiators, we documented 710 incident UC cases (65.41 UC/100,000 person-years) within this cohort. The multivariate-adjusted hazard ratios (HR) for risk of UC comparing current use of drospirenone to other progestin-based COCs was 0.99 (95% CI: 0.80, 1.25). Smoking was defined using ICD-9 V-codes (the best available information). Only 6% of the population was identified as smokers (a clear under-ascertainment). Results were unchanged for a wide range of sensitivity analyses and stratified by smoking status.

Conclusions: In a large cohort of COC-initiators, there is no association between current use of drospirenone and risk of incident UC as compared to other COCs. While it is possible that these results are confounded by smoking status, such effects would have to be large to disguise a substantial increase in risk.

364. Postmenopausal Estrogen Therapy Increases the Risk of Gallstone Disease – A Population-Based Case-Control Study

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Background: The decision to initiate postmenopausal estrogen therapy should be based on an assessment of associated benefits and risks. Estrogens increase the cholesterol-saturation of bile and may increase the risk of gallstone disease. However population-based evidence is sparse.

Objectives: To determine the association between postmenopausal estrogen therapy and gallstone risk.

Methods: We conducted a population-based case-control study using medical databases from Northern Denmark (1.7 million inhabitants). Cases of postmenopausal women (≥45 years) with gallstone disease were identified from the Danish National Registry of Patients (DNRP) in the period 1996–2010. For each case we selected 10 population controls using risk set sampling (matched on age and sex). Exposure to drugs containing estrogen was ascertained from the prescription database and cases/controls were categorized as current users if their last prescription was <90 days before diagnosis (or correspondent date for controls), or otherwise as former users. Co-morbidities were identified in the DNRP. Conditional logistic regression was used to estimate adjusted odds ratios (AORs) and 95% confidence intervals (Cls) of gallstone disease in women treated with estrogens.

Results: We identified 16,386 female gallstone patients and 163,860 matched controls (median age 65 years). A total of 4,437 cases (27.1%) and 33,162 controls (20.2%) had been exposed to estrogen corresponding to an AOR of 1.51 (95% Cl 1.45–1.56). One thousand five hundred twenty-three cases (9.3%) and 9,778 controls (6.0%) were current users of estrogen corresponding to an AOR of 1.76 (95% Cl 1.66–1.87). In former users the corresponding AOR was 1.40 (95% Cl 1.34–1.46) indicating a continued but less elevated risk.

Conclusions: Postmenopausal estrogen therapy was associated with an increased gallstone risk. This should be taken into consideration when deciding to initiate estrogen treatment in postmenopausal women.

365. The Safety of Oral Hormone Replacement Therapy: Final Results from the EURAS-HRT Study

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Background: Progestins used in HRT have substantially distinct pharmacological profiles. The novel progestin drospirenone (DRSP) has antimineralocorticoid properties which potentially could have beneficial as well as unfavorable effects on cardiovascular outcomes.

Objectives: To compare incidence rates of serious adverse events - in particular cardiovascular outcomes - in users of oral continuous combined preparations.

Methods: Prospective, controlled cohort study with three arms: women using (1) DRSP/estradiol, (2) other oral continuous-combined HRT (occHRT), and (3) all other oral HRTs. The study population included women aged 40 or older in seven European countries who started or switched to an oral HRT at time of inclusion in the study. Field work started in 2002 and ended in December 2010. All patient-reported outcomes of interest were validated by the women's treating physicians. A multifaceted 4-level follow-up procedure ensured low loss to follow-up rates.

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The final analysis is based on Cox regression models comparing the cohorts.

Results: A total of 30,597 users of oral HRT preparations - reflecting more than 101,000 WY of observation - were recruited by 1,052 study centers. The prevalence of cardiovascular risk factors among HRT users is higher in Northern and Central European countries than in Mediterranean countries. Incidence rates of DRSP/estradiol and low-dose occHRT for venous thromboembolic events were 17.5 (95% CI: 11.2–26.0) and 18.2 (95% CI: 11.9–26.6) per 10,000 WY, respectively. The respective incidence rates for arterial thromboembolism were 10.9 (95% CI: 6.1–18.0) and 29.8 (95% CI: 24.1–36.4) per 10,000 WY with a hazard ratio adjusted for age, BMI, hypertension, region, family history of fatal ATE, diabetes, user status of 0.5 (95%CI: 0.3–0.8) for DRSP/estradiol vs. other occHRT.

Conclusions: Results indicate a good safety profile with respect to cardiovascular risk for DRSP/estradiol compared to other occHRT preparations. Serious cardiovascular events occur less frequently in DRSP/estradiol users compared to users of other continuous-combined HRT.

366. Trends in Opioid Prescribing between 2000 and 2009 in Germany A Regional Claims Data Analysis

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Background: While during the 1990's the underuse of opioids for treatment of patients especially with cancer-pain has been criticized, it is now a topic of debate whether opioids are overprescribed for non-cancer pain.

Objectives: The aims of the study are to analyse the treatment prevalance for opioids during 2000 and 2009 and to compare prescribing for opioid recipients with and without cancer diagnosis.

Methods: *Database:* Claims data of a regional statutory health insurance fund (AOK Hesse). Study population in 2000: 326,598 insured (51% women, mean age: 43.9 year); in 2009: 264,982 insured (51.9% women; mean age 46.4 year). Opioids: ATC-Code N02A excl. codeine, codeine-combination, methadone. Prevalence: standardised to the population of Germany (31st December of the respective year). Patient with cancer: identified by ICD-10-GM code: C00-C97 excl. C44 documented in the claims data in the year of opioid prescription. Coverage of the first treatment episode for incident patients was assessed for outpatient days by calculating one DDD/day and allowing for a 30 day break.

Results: Between 2000 and 2009, opioid treatment prevalence increased by +34.7% from 3.31% (m: 2.68%, f: 3.90%) to 4.46% (m: 3.67%, f: 5.23%), DDD increased by +122.6%, DDD/user: +66.7%. In 2000 and 2009, 0.37% and 1.25% received strong opioids, respectively. Prevalence with sustained release/transdermal formulations increased significantly (2000: 1.03%, 2009: 3.03%). Most opioid recipients were treated for non-cancer pain (2000: 82.7%, 2009: 79.4%) In 2008, patients with cancer received to a lesser amount (84.4%) weak opioids as first prescription (non cancer: 90.7%). The percentage of incident opioid recipients with a first treatment episode of >90 days increased for those with cancer and non-cancer pain from 7.2% (2001) to 10.4% (2008; +44.4%) and from 3.9% to 7.4% (2008; +89.7%), respectively.

Conclusions: Within 10 years not only the number of recipients but also the amount of DDD per recipient increased. Opioids are mainly prescribed for non-cancer pain, a development that should be paid attention to especially concerning long term treatment, for which evidence of benefit is still lacking.

367. Dramatic Increases in the Use of Strong Opioids in the Elderly

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Background: Increasing use of strong opioids is reported. While strong opioids are important tools in the treatment of severe pain, their addictive nature raises a concern. Thus, the use of opioids needs to be carefully monitored in all age groups.

Objectives: To examine trends in opioid use in middle-aged and elderly Norwegians.

Methods: The study population consisted of Norwegians, aged 41–80, who had at least one prescription for strong opioids (morphine, oxycodone, buprenorphine, fentanyl, ketobemidone) during 2005–2010. Information was obtained from the NorPD database which registers all prescriptions filled in any pharmacy in Norway. Medications are coded using the WHO Anatomical, Therapeutic, Chemical (ATC) classification system.

Results: Opioid use in this age group increased substantially over the years of the study – from 4.1/1000 in 2005 to 11.7/1000 in 2010, or more than double. Much of the increase was due to drastic increases in use by the oldest age groups - for the age group 76–80 rates increased from 4.7/1000 in 2005 to 26.4/1000 in 2010, or more than five times. For individual opioids, the greatest increases were seen for oxycodone, at 3.8 times the annual rate from 2005 to 2010 and buprenorphine at 5.3 times the annual rate. Morphine showed little increase in use before 2009 but then a considerable increase for 2010. In 2010 morphine also showed an increase with age for the first time.

Conclusions: An increase in strong opioid use was seen for middle-aged and elderly Norwegians, especially in bu-

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prenorphine and oxycodone. The especially large jump in rates between 2009 and 2010 imply further increases in the future. Especially dramatic was the increase for the oldest age groups. The increasing availability of opioid patches for pain control may be at least partially related to these dramatic increases. One hopes that these increases signify better pain control for chronic pain in the elderly. However, careful monitoring for appropriate use is needed as this transition time in use of strong opioids will determine future use of opioids.

368. Risk of Unintentional Overdose Following Outpatient Opioid Treatment for Pain

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Background: Investigations of the risk of unintentional overdose among new users of opioid analgesics have not evaluated the risk specific to long-acting (LA) preparations in comparison to short acting (SA) preparations.

Objectives: To evaluate unintentional overdose following initiation of LA or SA opioid agents for acute and chronic pain control.

Methods: We identified all new users of outpatient LA and SA single-agent prescriptions in the VA Healthcare System between 2000 and 2009. Patients were followed until outcome [admission or ER visit for unintentional overdose (ICD-9 E850.x-858.x,E980.0, and 960.x-979.x)], or censoring by treatment cessation, agent switching, or death. Patients with a history of opioid use in the prior 6 months were excluded. Covariables included opioid indication, demographics, comorbid conditions, healthcare utilization and concomitant medications. Incidence rates (IR) and Hazard Ratios (HR) using Cox's PH regression [with multivariate and stabilized-IPTW adjusted estimates] were calculated, with stratification by <2weeks and >2weeks follow-up due to time-varying hazards.

Results: Two lakh fifty thousand nine hundred ninty-three patients received a new opioid prescription, 98% received SA (42% hydrocodone, 26% codeine, 20% oxycodone, 11% propoxephene, and 0.5% are other agents) and 2% received a LA (41% morphine, 24% fentanyl, 20% methadone, 15% sustained release oxycodone). Indications for SA were 58% chronic pain, 15% acute pain, 2% cancer and 25% other indication, and 65% chronic pain, 7% acute pain, 7% cancer and 21% other indication for LA. The IR for unintentional overdose was 17.3 events per 10,000 Person years (PY) for SA, and 41.5/10,000PY among LA. Overall use of LA was associated with an increased risk of overdose, HR = 2.24 (1.59,3.17) which was greater in the first two weeks of treatment HR = 4.61 (2.77, 7.66), thereafter HR = 1.64 (1.07,2.52). These effects were consistent across the indications and with IPTW adjustment.

Conclusions: Although uncommon as an initial prescription, LA agents were associated with increased risk of unintentional overdose, with the highest risk period in the first two weeks of treatment. Providers should use caution when administering these agents to opioid naive patients.

369. Can the EU-ADR Database Network Detect Timely Drug Safety Signals?

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Background: Several ongoing initiatives (e.g., EU-ADR) have been launched assuming that mining electronic medical records may detect drug safety signals earlier than was done in the traditional way.

Objectives: To test this hypothesis, we investigated if the signal concerning rofecoxib and acute myocardial infarction could have been identified in EU-ADR database network, much earlier than rofecoxib withdrawal (30th September 2004).

Methods: The EU-ADR network comprises of seven electronic medical record databases covering currently a population of 22 million patients from three European Countries during the years 1996–2010. Harmonized data extraction and analysis has been conducted in all databases through custom built software Jerboa, which allows for data aggregation and elaboration while databases remained locally. Dividing the time before rofecoxib withdrawal by quadrimestre, we measured the first point in time in which the signal concerning rofecoxib and AMI would have been identified in the EU-ADR network, considering on average one year time gap for updating of data from databases in the EU-ADR network. A signal was defined in EU-ADR as at least two-fold increase in the risk (statistically significant) for the association between AMI and rofecoxib using Longitudinal Gamma Poission Shrinkage.

Results: A total of 685 AMI cases exposed to rofecoxib were identified in the EU-ADR network during the years 2000–2004. In the third quadrimestre of 2000, the EU-ADR network was able to identify a strong signal concerning rofecoxib and AMI as 847,609 person-days of

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exposure to this drug was available. With data accumulated till that moment a Relative Risk of 4.46 (95% Confidence Interval: 2.84–6.72) was found.

Conclusions: This analysis shows that by using the EU-ADR database network a strong signal concerning rofecoxib and acute myocardial infarction could have been detected much earlier than rofecoxib withdrawal. Whether this holds prospectively for other signals will depend on the incidence of the event, the level of exposure and the lag time.

370. Drug Intoxication in Patients Registered for Liver Transplantation for Acute Liver Failure: Results from the 7-Country SALT Study

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Background: Intentional or non-intentional drug overdose may cause acute liver failure (ALF) leading to transplantation.

Objectives: To evaluate drug overdose cases identified in the SALT study.

Methods: SALT study was a multicentre, case-population study performed in France, Greece, Ireland, Italy, Netherlands, Portugal, and UK between 2005 and 2007 in adults. Data on ALF cases were sought through liver transplant registries and hospital records. ALF cases were classified as (1) with an identified clinical cause (were not further considered for drug exposure), (2) exposed to drugs (including herbal and homeopathic medicines) within 30 days of index date (ID, initial symptoms of liver disease). Drug-exposed cases were again subdivided into (1) acute drug intoxication (ADI), with or without suicidal intent, (2) non-ADI. Demographic, clinical, and drug use data in the 30 days prior to ID were collected for all drug-exposed ALF cases. Drug-exposed cases of ALF were assessed individually by a case adjudication committee using WHO causality scale.

Results: Fifty-two (91%) of the 57 eligible transplant centres contributed data. A total of 9,479 cases registered for transplantation at the contributing centres, of which 600 were ALF, and 301 were exposed to a drug within 30 days prior to ID. Of these, 114 were ADI (72 intentional, 10 non-intentional, 32 intentionality not clearly defined). ADI was responsible for 20% of all cause ALF in the seven participating countries; the highest in Ireland (52%), followed by the UK (28%), France (18%), the Netherlands (8%), Italy (1%). No ADI cases of ALF were identified in Greece and Portugal. ADI were mostly females (61%), mean age 33.6 (±Std 10.9) years. One hundred eleven (97%) of the 114 ADI cases had been exposed to paracetamol, all had the causality score possible, probable or highly probable. Thirty-one (27%) ADI cases were exposed to antidepressants, and 30 (26%) to psycholeptics. For the three non-paracetamol cases, causal drugs were benzodiazepin derivatives + opioids, ectasy, and diclofenac + iron.

Conclusions: Paracetamol overdose with or without suicidal intent represented 97.4% of all intoxication drug-related ALF.

371. Effect of Regulatory Measures on Nimesulide Utilization in the Lisbon Region

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Background: Nimesulide has been associated with increased risk of hepatotoxicity. This prompted regulatory action by the European Medicines Agency. The following measures were applied in Portugal in 2011: change in product approved indications (January), a "dear doctor" letter (March), and removal of packages for therapies longer than 15 days (up to June).

Objectives: To quantify the effect of regulatory measures in nimesulide utilization in the Lisbon region.

Methods: We conducted a retrospective time-series analysis of billing records in the National Health Service in the Lisbon region (4.4 million patients). We gathered data on all oral non-steroidal anti-inflammatory drugs (NSAIDs) between January 2006 and November 2011 with monthly intervals. The main outcome was the proportion of nimesulide daily defined doses (DDD) billed for the total of oral NSAIDs (market share). We used autoregressive integrated moving average (ARIMA) to create a forecasting model from utilization data up to January 2011 (first regulatory measure), and predicted nimesulide utilization in the following months with 95% confidence intervals, which was then compared with actual data.

Results: Nimesulide was the NSAID with most DDDs billed from January 2006 to March 2007, with an average 22.3% market share (203.7 DDDs/1000 patients/month). Utilization dropped suddenly between April and June

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2007 (at that time the drug was removed from market in Ireland) and in the last semester of 2007 it had a market share of 14.2%. We therefore included into our model only data from June 2007 to January 2011. Best fit was achieved with an ARIMA(0, 1, 0) (1, 0, 0) model (R-squared 0.915; Ljung-Box Q statistic p = 0.957). Observed nimesulide market share decreased from 13.1% in January 2011, to a nadir of 6.6% in July, and then slowly increased to 7.3% in November (fifth in NSAID market share that month). Observed data fell and remained below the lower confidence limit of our model from April onwards.

Conclusions: Upon regulatory intervention, nimesulide utilization was significantly reduced in a manner not explained by chance or previous trends. However, it remained a highly used NSAID and market share seems to be increasing.

372. Are Low-Cost Generic Prescriptions Faithfully Captured in United States Pharmacy Claims Databases?

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Background: Many chain pharmacies in the United States have introduced four-dollar generic drug programs beginning in September 2006, representing some of the most widely used generic drugs. Because patients may pay out-of-pocket for medications purchased through these programs, concerns have been raised that some commercial pharmacy claims databases may not capture low-cost generic prescriptions.

Objectives: To evaluate the potential for missing drug claims after the initiation of the four-dollar generic program, by studying secular trends in warfarin filling among patients receiving regular international normalized ratio (INR) tests.

Methods: The MarketScan Research Database, a large national insurance database, was examined for the completeness of warfarin drug claims. Because patients on warfarin receive regular INR tests, and INRs are not regularly ordered on patients without concomitant use, this drug was ideal to examine pharmacy claims completeness. In each calendar quarter from 2003 to 2009, continuously-enrolled patients with at least two atrial fibrillation diagnoses and at least two outpatient INR tests were identified. Patients were also required to have at least six total months of continuous eligibility, be without hepatic dysfunction, and have pharmacy insurance benefits, filling at least one prescription in the quarter. Trends in the percentage of patients with prescription claims for generic warfarin and brand-name Coumadin were compared per calendar year and quarter to assess the policy's effect.

Results: Out of 377,879 patient-quarters, the percentage of drug claims per patient for each calendar quarter decreased slightly from 85.85% (95% CI: 84.97, 86.73) in 2003 quarter 1–84.12% (95% CI: 83.45, 84.79) in 2006 quarter 3. After the programs' introduction, the percentage decreased more substantially to 80.67% (95% CI: 80.15, 81.19) in 2009 quarter 4. Calendar years showed parallel trends and similarities across demographic characteristics.

Conclusions: Our study showed a very small decrease in warfarin filling after the introduction of the low-cost generic prescription drug programs, suggesting that the problem of missing claims is at worst small.

373. Extraction of Electronic Health Record Data in a Hospital Setting: Comparison of Automatic and Semi-Automatic Methods Using Anti-TNF Therapy as Model

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Background: Electronic health records (EHR) with integrated prescribing modules offers new possibilities to monitor drug utilization using the individual patient as the unit of analysis. Several studies have demonstrated extractions of drug information in primary care. There is limited experience and methods for extractions of drug therapy data in the hospital setting. Since most new drug therapies are introduced in hospitals there is a need to develop methods to study the quality and safety of drug therapy in the hospital setting.

Objectives: We evaluated the completeness and consistency of a generic automatic vs. a semi-automatic model for studying drug prescribing and dispensing of the TNF inhibitor infliximab (TNFi) across different diagnoses using a hospital based EHR-system.

Methods: This generic model builds on clinical information generated at Karolinska University Hospital (Stockholm, Sweden) by its EHR-system TakeCare®. Using two different extraction procedures, all administered infusions of infliximab during 2007–2010 were extracted from a relational database linked to the EHR-system. Extracted data included encrypted personal identity number, date of birth, sex, time of prescription, time of administration, healthcare units, prescribed and administered dose, time of admission and time of discharge. The primary diagnosis

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(ICD-10) for the treatment with infliximab was also extracted by linking inflixmab infusions to their corresponding treatment episode. The analyses focused on prevalence of use, diagnostic and dosage patterns.

Results: A total of 13,590 infusions of infliximab were administered during 2007–2010. Of those were 13,531 (99.6%) possible to link to a corresponding treatment episode and a primary diagnosis was extracted for 13,530 (>99.9%) infusions. Calculable information about dosage was found for 13,300 (98.3%) of all linked infusions.

Conclusions: This study shows the potential of monitoring drug therapy based on extractions from EHR. Extracted data can be linked to other clinical data with highly automatic methods to assess effectiveness and safety of drug therapies, providing data for quality assessment as well as research of drug therapy in clinical practice.

374. Impact of Exposure Misclassification Due to Incomplete Drug Data in Observational Studies of Safety and Effectiveness

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Background: Non-benefit drug use is often missing from administrative databases, potentially introducing bias in drug safety and effectiveness studies.

Objectives: To measure the effect of non-benefit drug use on observed associations between exposure and outcome, thereby documenting the potential magnitude of biases introduced when exposure status is misclassified from non-benefit drug use.

Methods: Among incident diabetic patients in Saskatchewan, Canada, users of benefit and non-benefit thiazolidinediones (TZDs), clopidogrel, and beta-blockers were identified in 2006 and followed until 2008. Differences in all-cause hospitalization or death between users of benefit and non-benefit drugs were evaluated using multivariable proportional hazards models. Bias was assessed by evaluating bootstrapped differences in risk estimates obtained from analyses containing non-benefit and benefit drug use vs. benefit drugs alone.

Results: We identified 5759 TZD users (28% non-benefit), 1551 clopidogrel users (24% non-benefit), and 351 beta-blocker users (42% non-benefit). Users of benefit drugs were more likely to be hospitalized or die than users of non-benefit TZDs (1515 [36%] vs. 420 [26%]; adjusted hazard ratio [aHR] 1.13, 95% CI 1.01–1.26), but not clopidogrel (642 [54%] vs. 171 [46%]; aHR 1.00, 95% CI 0.81–1.24) or beta-blockers (126 [62%] vs. 73 [49%]; aHR 1.30, 95% CI 0.88–1.91). Comparing the analyses with (benefit drugs only) and without (addition of non-benefit drugs) drug exposure misclassification suggested minimal bias was introduced for estimated risk of hospitalization or death for TZD [bootstrapped aHR difference +0.05, 95% CI 0.02–0.08], clopidogrel [+0.01, 95% CI -0.04 to 0.06], or beta-blockers [+0.06, 95% CI -0.09 to 0.20]).

Conclusions: Exposure misclassification from non-benefit drug use is common. Although patient characteristics and outcomes differed between users of non-benefit and benefit drugs, misclassification of drug exposure did not meaningfully bias estimates of risk in our study.

375. Drug Exposure Misclassification Because of Prior-Authorization Policies: A Cautionary Tale for Researchers Using Databases Limited to Formulary-Approved Prescriptions

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Background: Administrative databases often only capture prescription claims approved on the formulary. Automated changes in claims adjudications may impact the completeness of drug exposure information.

Objectives: To assess the impact of automating a prior-authorization policy on the completeness of prescription claims data we took advantage of a natural experiment in Saskatchewan, Canada.

Methods: Weekly counts of formulary-approved and total prescription claims in 2006 for new-users of antidiabetic agents were examined across four antidiabetic drug categories: thiazolidinediones (TZDs), metformin, glyburide, and insulin. On July 1st, 2006, Saskatchewan's public drug plan implemented an automated, online adjudicated, prior-authorization process for TZDs; where as previously prior-approval was paper-based. No policy changes occurred for metformin, glyburide, or insulin. We estimated the effect of this policy change using interrupted time-series analyses with autoregressive integrated moving average models.

Results: We examined 223,552 prescription claims in 2006. The number of formulary-approved prescription claims for TZDs increased immediately after the automated prior-authorization process was introduced by 240 prescriptions per week (95% CI 200–280, $p < 0.001$). Total prescription claims for TZDs did not change following the policy interruption ($p = 0.95$). The average proportion of TZD formulary-approved claims was 73% before and increased to 93% immediately following policy change (19.5% absolute change, 95% CI 18.7–20.4%). No change in formulary-approved or total prescription claims was observed following the policy interruption for metformin, glyburide, or insulin ($p > 0.1$ for all).

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Conclusions: Automation of the prior-authorization policy immediately increased the proportion of captured formulary-approved TZD claims, indicating a substantial portion of TZD use was previously un-captured. Administrative databases that only capture formulary-approved drugs systematically underestimate exposure because they are incomplete with respect to prior-authorization drug data.

376. Trajectory Models: A New Approach to Classifying and Predicting Long-Term Medication Adherence

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Background: Predicting medication adherence is important for efficiently targeting adherence improvement interventions. Group-based trajectory models identify groups of patients with similar patterns of adherence that may be more accurate and efficient than conventional measures such as proportion of days covered (PDC).

Objectives: To evaluate the use of group-based trajectory models for classifying patients by their long-term adherence to statins compared with other adherence measures, and to determine at what point following the initiation of treatment a patient's trajectory group can be accurately predicted.

Methods: We used prescription claims data from CVS Caremark and included patients that filled at least one prescription for a statin medication between June 1, 2006 and May 30, 2007. Patients were required to have continuous drug insurance benefits for 1 year before and 15 months after the date of first statin fill. Patients that received any statin prescription via mail order were excluded. We used C-statistics to compare each adherence summary, including PDC, PDC dichotomized at ≥/ <80%, and trajectory models with 2–6 groups, with the raw adherence pattern, defined by the 15 monthly indicators of ≥24 days covered. We compared the six-group misclassification rates from multinomial logistic regression models predicting trajectory classification vs. a linear regression predicting PDC.

Results: In 289,971 statin initiators, the six-group trajectory model summarized long-term adherence best (C = 0.938), while PDC and dichotomized PDC summarized less well (C = 0.881 and 0.762, respectively). Correct prediction was 1.3 times higher for trajectory grouping compared with PDC. Correct prediction of trajectory group was 2.2 times higher when models included information up to 6 months post-initiation compared with baseline.

Conclusions: A six-group trajectory model summarized long-term adherence patterns better than traditional approaches and was better predicted by the baseline covariates. Group-based trajectory models may facilitate targeting of interventions and may be useful for adjusting for confounding by health-seeking behavior.

377. Non-Adherence to Chronic Drug Regimens When Costs Increase: Expected Drug Use and Non-Linear Cost-Sharing Effects

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Background: Many health insurance plans require variable amounts of patient cost-sharing during the year based on individual expenditures, e.g., Medicare coverage gaps. These endogenous cost-sharing changes complicate any evaluation of drug use.

Objectives: We examine use of two types of chronic drug regimens among Medicare beneficiaries enrolled in plans with consistent cost-sharing (no coverage gap) in 2006 and a coverage gap in 2007.

Methods: We examined chronic drug treatment adherence as a function of expected annual drug spending in Medicare beneficiaries continuously enrolled in a Part D Prescription Drug Plan (2006–2007) who received a lipid (n = 18,650) or diabetes (n = 10,033) drug in January 2006. We used expected spending to estimate drug use absent endogenous changes due to cost-sharing. Using logistic regression models with patient fixed effects, we examined adherence based on drug supply, stratified by expected annual spending. In random effects models, we examined characteristics associated with lower than expected spending. We examined expected and actual drug spending in 2006 when beneficiaries did not have a coverage gap as a falsification test.

Results: Most subjects expected to enter the gap did (94%), but among subjects entering the gap, many expected to exit the gap did not (e.g., 28% of diabetes drug users). Among those who did not exit the gap as expected, the odds of non-adherence increased substantially during vs. before the gap (e.g., OR = 1.44 [1.18–1.75] for lipid drugs). After exiting the gap, there were slight, non-significant decreases in non-adherence (e.g., OR = 0.92 [0.74–1.14] for lipid drugs). Being female, younger age, and using fewer drug classes were associated with lower than expected drug use and persistent non-adherence after exiting the gap. When subjects did not face a gap (2006), there were no differences in adherence before and after reaching the coverage gap thresholds.

Conclusions: Many patients with substantial drug burden become non-adherent to their drug regimens with mid-year cost-sharing increases.

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378. Comparing Measures of Regularity of NSAID Dispensings Based on Register Data

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Background: Exposure patterns are important when assessing safety and effectiveness. NSAID exposure varies from sporadic to chronic use, which may be affected by indication and course of symptoms. Prescription register data only contain information on time and amount dispensed. It is important to develop methods to characterize regular dispensing patterns based on this information.

Objectives: To explore patterns of NSAID use and evaluate two different ways of measure regular dispensing three dimensions.

Methods: In the Swedish Prescribed Drug Register we identified 556,011 incident users of NSAIDs 2007–2010. All had complete follow-up for 3 years (1,430,661 dispensings). We obtained information on dates for all dispensings, number of DDDs dispensed, age and sex. The average dose was estimated as number of DDDs dispensed divided by number of days to next dispensing. For persons dispensed NSAIDs at least three times, we assessed regularity of dispensing in terms of three dimensions, inter-prescription time, amount dispensed, and average dose using two different measures. Firstly we calculated the ratio between the sum of all deviations divided by the sum of all observations. Secondly, the standard deviation was calculated. Persons were classified as regular users if the measure was below the 30th percentile.

Results: The number of dispensings per person was median (IQR) two (1–3). One lakhs seventy two thousand two hundred ninty-three were dispensed NSAIDs at least three times. Number of persons that were classified as regular users was for inter-prescription time, amount and average dose, 51,630, 34,524 and 51,679 respectively with the 1st measure and 51,618, 34,549 and 51,652 respectively with the 2nd measure. Dispensing patterns were classified as regular for 5% of the users in all three dimensions using the 1st measure, and for 8.2% using the 2nd measure. When looking at amount dispensed, 29% had an extreme regular pattern (regularity measure < 0.05). The same number when looking at inter-prescription times and average dose were $< 2\%$ for both.

Conclusions: The two different ways to calculate regularity were comparable. When examining inter-prescription times and average dose, the patterns were more irregular compared to dispensed amount.

379. Impact of Case Validation on Incidence Rates of Upper Gastrointestinal Complications

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Background: In a systematic review (Lin KJ et al., 2011) incidence rates (IR) of peptic ulcer disease from studies validating cases by medical chart review were lower compared to studies without validation. Evaluations of the impact of validation in actual studies are scarce.

Objectives: To assess the impact of case validation strategies, used in published studies, on IR of Upper Gastrointestinal complications (UGIC) in users of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Methods: A population-based study using health databases and hospital charts of Friuli Venezia Giulia, Italy, included all residents receiving NSAIDs during 2001–2008. Potential cases identified by primary hospital discharge ICD-9-CM site- and lesion-specific (531 gastric ulcer, 532 duodenal ulcer, 533 peptic ulcer, 534 gastrojejunal ulcer) and nonspecific (578 gastrointestinal hemorrhage) codes were validated by hospital chart review. Positive Predictive Value (PPV) was above 95% for 531 and 532, 81.4% for 533 and 534 and 40.2% for 578. We estimated crude IRs with Poisson 95% confidence interval (95%CI) of UGIC applying strategies used in previously published studies for case inclusion:

1. All cases identified by codes 531, 532 (high PPV) and the confirmed cases identified by 533, 534, 578 (low PPV).
2. All potential cases identified (without validation).
3. All cases identified by codes 531, 532 (high PPV).

Results: The cohort had 588,827 users, 2,959,555 person-years of follow-up, and 4,014 potential cases. Using strategy 1 (validation of low PPV codes) the IR was 0.97 (95%CI 0.94–1.01) per 1,000 person-years. Compared with strategy 1, inclusion of all potential cases (no validation, strategy 2) increased the IR by 39.2% (IR = 1.36; 95%CI 1.31–1.40); inclusion of only cases with codes 531, 532 (high PPV, strategy 3) decreased the IR by 29.5% (IR = 0.69; 95%CI 0,66–0,72).

Conclusions: In this cohort case validation had major impact on IR estimates. Including all potential cases without validation overestimated the IR by 39%. Including only cases with site-specific high PPV codes underestimated the IRs by about 30%. To avoid IR under or overestimation all codes are required and validation of nonspecific codes is essential.

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380. Risk of Acute Liver Failure Leading to Transplantation after NSAID or Paracetamol Exposure: Final Results of the seven European-Country Study of Acute Liver Transplant (SALT)

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Background: NSAIDs and paracetamol are thought to be common causes of ALF leading to liver transplantation (LT).

Objectives: To estimate the risk of ALF leading to registration for LT in patients without identified clinical etiology and exposed to NSAIDs and paracetamol.

Methods: Multicentre, case-population study performed in France, Greece, Ireland, Italy, Netherlands, Portugal, and UK between 2005 and 2007 in adults. Patients were identified by national/local LT registries. Demographic, clinical, and drug use data were collected for ALF cases without identified clinical etiology (ICE). Exposure to NSAID or paracetamol was determined within 30 days prior to initial symptoms of liver disease. Rate per million treatment-years (tt-yrs) was calculated using sales data from IMS.

Results: Of the 62 LT centers, 57 were eligible, and 52 contributed data. Among the 9479 patients identified from LT lists for the 3-year period, 600 (6%) were ALF: 219 (36% of all-cause ALF) had an ICE, 18 (3% of all-cause ALF) had unavailable medical files, 62 (11%) were not drug-exposed and had no ICE, and 301 (52%) were drug-exposed without ICE. Among the latter, 40 (7% of analyzable ALF) were exposed to NSAIDs, mean age 43.9 years, 29 (72%) female. Event rates per million tt-yrs were 4.78 (95%CI, 3.42–6.51) for all NSAIDs pooled, 6.84 (3.64–11.69) for ibuprofen, 5.64 (2.43–11.11) for nimesulide, 4.66 (1.71–10.14) for diclofenac, 4.64 (0.96–13.56) for ketoprofen, and 4.89 (0.59–17.66) for naproxen. Event rate for non-over dose paracetamol was 9.93 (7.89–12.34), and 23.53 (20.32–27.11) when intentional or non-intentional overdoses were included. Event rates for all NSAID pooled were 3.9 (95%CI 1.2–12.5) times higher in Ireland than in all countries pooled, than all countries pooled.

Conclusions: The risk of ALF leading to registration for liver transplantation was rare and showed no differences among the most used NSAIDs. Non-overdose paracetamol-exposed ALF was twice more common than NSAID-exposed ALF.

381. Proton Pump Inhibitors and Traditional Nonsteroidal Anti-Inflammatory Drugs and the Risk of Acute Interstitial Nephritis and Acute Kidney Injury

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Background: Numerous case reports and case series have implicated proton pump inhibitors (PPIs) as agents that may elicit an acute interstitial nephritis (AIN) hypersensitivity reaction. Concomitant use of PPIs and traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) is increasing. Therefore, elucidating these drugs' deleterious effects on the kidney, alone and in combination, is warranted.

Objectives: To examine the associations between PPIs, tNSAIDs, and PPI + tNSAID co-exposure and the development of: (1) AIN, a specific kidney injury often attributed to these drugs; and (2) acute kidney injury (AKI), a general kidney injury encompassing AIN.

Methods: Two retrospective case-control studies were conducted, one for each outcome, within the United Kingdom's General Practice Research Database. Cases were diagnostic-coded AIN (primary outcome) or AKI (secondary outcome) events. Controls were matched on age,

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sex, and general practitioner practice. Exposures were defined by the presence/absence of the following mutually-exclusive therapies on the index date: (1) PPI alone; (2) NSAID alone; (3) PPI + tNSAID; or (4) neither PPI nor tNSAID (referent).

Results: Sixty-eight AIN cases and 3,347 controls were identified. The unadjusted odds ratios (ORs) for PPI and tNSAID exposures alone were 6.15 (95% confidence interval: 2.29–16.53) and 1.93 (0.81–4.60), respectively. The adjusted ORs were 3.20 (0.80–12.79) and 1.90 (0.65–5.51), respectively. Twenty seven thousand nine hundred eighty-two AKI cases and 1,323,850 controls were identified. The unadjusted ORs for PPI alone, tNSAID alone, and PPI + tNSAID exposures were 2.09 (1.94–2.25), 1.90 (1.82–1.98), and 3.02 (2.47–3.70), respectively. The adjusted ORs were 1.05 (0.97–1.14), 1.31 (1.25–1.37), and 1.33 (1.07–1.64), respectively.

Conclusions: PPI exposure may increase the odds of AIN, although this should be confirmed in a dataset with more AIN cases to allow for increased statistical precision. tNSAIDs, yet not PPIs, were associated with a significantly increased odds of AKI.

382. Risk of Ischemic Stroke Associated with the Use of Individual Non-Steroidal Anti-Inflammatory Drugs

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Background: The EU funded Safety of Non-Steroidal Anti-Inflammatory Drugs project aims to estimate the risk associated with individual NSAIDs and to develop decision models for physicians and regulators. Within this project a meta-analysis of observational studies suggested an increased risk of ischemic stroke associated with the use of diclofenac and rofecoxib. Limited evidence was available for other individual NSAIDs.

Objectives: To estimate the risk of ischemic stroke associated with the use of individual NSAIDs.

Methods: Under a common protocol data was obtained from six databases (DBs) covering four European countries: Netherlands (IPCI, PHARMO), Italy (SISR, OSSIFF), Germany (GePaRD) and UK (THIN). For each DB a matched case-control study nested in a new NSAID-user cohort was performed. Cases of stroke were matched on sex, age and index day to up to 100 controls. Demographic and lifestyle information, comorbidities and concomitant drug use were considered as potential confounders. Past users, i.e., cohort members whose exposure period ended ≥184 days before the index date, were used as reference. Adjusted odds ratios (ORs) for current use of individual NSAIDs and their 95% confidence intervals were estimated using conditional logistic regression.

Results: Preliminary results based on currently available data from four of the six DBs including 44,440 cases of ischemic stroke found ORs of 1.4 (95% CI = 1.3–1.6, GePaRD), 1.1 (0.3–3.5, PHARMO), 1.3 (1.1–1.5, OSSIFF) and 1.3 (1.2–1.4, SISR) for current use of diclofenac compared to past use and ORs of 1.2 (1.1–1.5, GePaRD), 1.7 (0.4–7.0, PHARMO), 1.1 (0.9–1.5, OSSIFF) and 1.3 (1.2–1.4, SISR) for current use of ibuprofen. In SISR ORs of 1.5 (1.3–1.7) and 1.4 (1.3–1.6) were observed for rofecoxib and etoricoxib. Numbers of cases exposed to coxibs were too small in other DBs.

Conclusions: These preliminary analyses suggest an increased risk of ischemic stroke with the current use of diclofenac, ibuprofen, rofecoxib and etoricoxib. Pooling of data from all DBs is necessary to evaluate the risk of less frequently used NSAIDS, the effect of dose, duration and potential other effect modifiers and separately for other subtypes of stroke.

383. Nonsteroidal Anti-Inflammatory Drug Use and Brain Tumour Risk: A Nested Case-Control Study in the General Practice Research Database

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Background: Case-control and experimental studies have highlighted an inverse association between regular use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and brain tumour risk, particularly gliomas. To date, prospective analysis has not supported these findings but these have been based on self-reported drug use.

Objectives: To investigate the association between NSAID/aspirin use and risk of brain tumour subtypes in adults using anonymous longitudinal General Practitioner (GP) medical records.

Methods: A nested case-control study was conducted within the UK General Practice Research Database (GPRD). Cases with recorded primary brain tumour

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codes (n = 5365) diagnosed between September 1987 and April 2009 were matched to 52,599 controls on GP practice site, gender and year of birth. Exposure to aspirin and non-aspirin NSAID use was expressed as Defined Daily Doses (DDDs). Conditional logistic regression analyses was used to calculate odds ratios (OR) and 95% confidence intervals (CI) associated with NSAID/aspirin use compared with non use.

Results: Mean follow-up time was 7.2 years. The dose (DDDs) and duration (days) of NSAID/aspirin use per patient (excluding the year prior to diagnosis) was divided into fifths to compare the highest DDD use to no use. All analyses were adjusted for smoking, BMI, hay fever, eczema, rheumatoid arthritis and diabetes. There was no association between aspirin/NSAID use and overall brain cancer risk OR 1.08 (95% CI 0.91, 1.27) or individual brain tumour subtypes. Similarly in NSAID only analysis, no association was observed with overall brain tumour risk OR 1.09 (95% CI 0.93, 1.30) or other brain tumour subtypes (meningioma, glioma, other brain). When additionally controlled for high dose aspirin use, there was no significant association between aspirin and overall brain tumour risk OR 0.84 (95% CI 0.62–1.13) or other brain tumour subtypes.

Conclusions: Findings from this large nested case-control study do not support a protective association with NSAID/aspirin use and brain tumour risk.

384. Medication Use and Hospital Admission Rates among Preterm Born Children Compared to Full Term Born Infants

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Background: About 5–12% of all pregnancies in western countries result in preterm births. Preterm born infants may be at increased risk of adverse outcomes.

Objectives: To compare hospitalization and medication use in the first year of life between preterm and full term born infants.

Methods: Data for this retrospective cohort study were obtained from linking the PHARMO record linkage system, which includes detailed information on drug dispensing and hospitalization histories, and The Netherlands Perinatal Registry, including perinatal medical case records. From this linked cohort, all preterm born infants (gestational age < 37 weeks) between 2004 and 2007 were randomly matched to 4 full term born infants on gender, month and year of birth. All infants were followed from birth until end of data collection in PHARMO RLS, December 31st 2008 or until their first birthday, whichever occurred first. During follow-up, hospitalization and medication use was assessed. Cox proportional hazard regression models were used to estimate the relative risk of hospitalization/medication use among preterms compared to full terms. Population attributable risk percentages (PAR%) were calculated to estimate the proportion of hospitalization/medication use attributable to prematurity.

Results: Among the 71,607 singletons born between 2004 and 2007, 4,277 (6%) were born preterm of which 90% were hospitalized at birth, compared to 55% of the full terms. Premature infants were twice more likely to be re-hospitalized (RR 2.0; 95% CI 1.9–2.2), specifically for respiratory related diseases. Prematurity accounted for 6% of respiratory re-admissions. In the second half year of life, the most frequent observed outpatient drugs were antibacterials for systemic use, and drugs for obstructive airway diseases. Premature infants were 50% more likely to receive respiratory medication (RR 1.5; 95% CI 1.4–1.7). Corresponding PAR% was 3%.

Conclusions: In the first year of life, preterm born infants are up to 2.0 times more likely than full term borns to be hospitalized or use medication, especially related to respiratory disease.

385. Initial Findings from the Anti-Psychotics, Keep It Documented for Safety (A + KIDS) Medication Registry for North Carolina Medicaid Youth

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Background: The dramatic rise in usage of anti-psychotics among United States children is well documented. Compliance rates with current safety monitoring guidelines are known to be low. In response to these concerns, the North Carolina Division of Medical Assistance established the Antipsychotics-Keeping it Documented for Safety (A + KIDS) registry.

Objectives: This report focuses on findings related to the initial objectives of the A + KIDS project: (1) establish a web-based safety registry successfully as determined by provider participation and (2) obtain and evaluate clinical information derived from the registry.

Methods: In April, 2011 A + KIDS began asking prescribers of anti-psychotics for children twelve and under to

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respond to a set of questions regarding dose, indication, and usage history. Registry authorizations were examined by linking Medicaid prescription claims to registry entries. A hierarchical ranking system of primary diagnosis and target symptom was used to classify and describe indications. Providers were classified into different types and the number of patients and authorizations per provider were examined.

Results: In the initial 6 months, 730 providers registered 5,532 patients, 19% below age seven. Authorized fills accounted for 6% of total fills in month one, but 72% of fills by month six. Top diagnosis groups for registrants were Unspecified Mood Disorder, Autism Spectrum Disorder, and Disruptive Behavior Disorder. Top symptoms were aggression, irritability, and impulsivity. Psychosis accounted for 5% of the target symptoms. Twenty-nine per cent of children were in no form of psychotherapy. Physician assistants had a mean 10.7 authorizations per provider compared to 8.7 for medical doctors. Twenty-five per cent of providers were responsible for 81% of authorizations.

Conclusions: The A + KIDS registry initiative was successful as measured by rapid provider uptake. The registry provided a rich source of clinical information not available from claims data alone. With the addition of the adolescent cohort and provider-entered metabolic data, A + KIDS will allow for detailed examinations of antipsychotic utilization, safety, and guideline compliance.

386. Influence of Relative Age on Diagnosis and Treatment of Attention-Deficit/Hyperactivity Disorder in Children

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Background: The potential effect of children's relative age within grade on treatment and diagnosis of attention-deficit/hyperactivity disorder (ADHD) has been little studied, particularly outside the United States.

Objectives: To determine the influence of relative age within grade on diagnosis and prescription drug treatment for ADHD. We hypothesized that the younger children within each grade would be more likely to be diagnosed with ADHD and to be prescribed ADHD medications.

Methods: We conducted a cohort study involving 937,943 children in British Columbia, Canada, who were 6–12 years of age at any time from December 1, 1997, to November 30, 2008. The cut-off birth date for entry into school is December 31 in British Columbia, so children born in December are typically the youngest in their grade. We calculated the absolute and relative risk of being diagnosed with ADHD and of receiving a prescription for methylphenidate, dextroamphetamine, amphetamine or atomoxetine for children born in December compared to children born in January.

Results: Boys who were born in December were 30% (relative risk [RR] 1.30; 95% CI: 1.23–1.37) more likely to be diagnosed with ADHD than boys born in January. Girls were 70% (RR 1.70; CI: 1.53–1.88) more likely to be diagnosed with ADHD if born in December compared to January. Similarly, boys were 41% more likely (RR 1.41; CI: 1.33–1.50) and girls 77% (RR 1.77; CI: 1.57–2.00) more likely to be prescribed an ADHD medication if born in December compared to January. If they were born in December as compared to January, the percentage of children diagnosed with the disorder was 1.71% (CI: 1.36–2.05%) greater for boys and 1.09% (CI: 0.88–1.30%) greater for girls, and the percentage of children prescribed an ADHD medication was 1.80% (CI: 1.48–2.11%) greater for boys and 0.84% (CI: 0.66–1.01%) greater for girls.

Conclusions: Our analyses provide evidence of a relative age effect in the diagnosis and treatment of ADHD in children in British Columbia. These findings raise concerns about potential harms from over-diagnosis and over-prescribing, which include adverse effects on sleep, appetite and growth, and increased risk of cardiovascular events.

387. Pediatric Acute Liver Injury: Signal Detection Using Multiple Healthcare Databases from EU-ADR Network

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Background: Data mining in spontaneous reporting system showed that drug-induced acute liver injury (ALI) is

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infrequently reported in pediatrics, but this system remains far from adequate for signal detection. EU-ADR project is aimed to develop and validate a computerized system combining data from multiple European electronic healthcare records (EHR) for early detection of drug safety signals.

Objectives: To identify drugs potentially associated with pediatric ALI using the EU-ADR network and to estimate the power of such a network for signal detection concerning pediatric ALI.

Methods: We extracted data on ALI cases and prescribed/dispensed drugs for individuals 0–18 years old registered within seven European population-based EHR/claims databases of the EU-ADR network during the years 1996–2008. Based on the background IR of ALI, power = 80%, alpha = 5% and the number of person-years (PYs) of drug exposure by ATC classification, we estimated the minimal required drug exposure to detect a signal concerning pediatric ALI. We identified these signals by measuring age- and sex-adjusted RRs, using all other drugs as comparator. Signals due to protopathic bias were discarded through the newly-developed LEOPARD method.

Results: Overall 4,838,146 children 0–18 years old contributed 25,601,011 PYs of follow-up time to the EU-ADR database network. Among them, 1,015 events of ALI were identified. The IR of pediatric ALI was estimated to be 3.96 (3.73–4.21)/100,000 PYs. The total amount of drug exposure that is required to detect a weak, moderate and strong association (RR≥1.5, 2.0, and 4.0) with pediatric ALI was 721,437 PYs, 202,498 PYs, and 31,005 PYs, respectively. Nine drugs have been found to be significantly (p-value <0.05) associated with pediatric ALI: metoclopramide, domperidone, phenoxymethylpenicillin, erythromycin, valproic acid, amoxicillin, clarithromycin, flunisolide and cefaclor.

Conclusions: Combining multiple EHR may facilitate the identification of potentially drug-induced ALI and increase the power for drug safety signal detection in pediatrics. Except for flunisolide, potential signals of pediatric ALI detected in EU-ADR are known to be hepatotoxic in adults.

388. Determinants of Atomoxetine and Central Nervous System Stimulant Treatment Initiation

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Background: Atomoxetine and central nervous system (CNS) stimulants have different safety profiles, yet similar indications. Determinants of initial pharmacotherapy selection in general practice remain unknown.

Objectives: To analyze clinical and sociodemographic determinants of initiation of psychotropic pharmacotherapy in youth.

Methods: The study utilized a population-based retrospective cohort. The cohort comprised 356,158 youths, 6 to 18 years of age, eligible for Medicaid fee-for-service benefits in 28 US states and atomoxetine or CNS stimulant initiation between 2003 and 2006. A logistic regression model was used to assess associations between selection of atomoxetine versus CNS stimulant and for sociodemographic and clinical characteristics in the preceding six month.

Results: 77,109 patients initiated atomoxetine treatment and 279,076 started CNS stimulants at an average age of 10.1 (Stdev 3.2). The propensity for atomoxetine initiation increased continuously with increasing age, (adjusted odds ration [OR]= 1.61, 95% CI 1.57-1.66) in age 15 to 19, compared to age 6 to 9. Substance use disorder (OR 1.54, 95% CI 1.43-1.66), tic disorder (OR 3.22, 95% CI 2.85-3.65) and disability (OR 1.35, 95% CI 1.29-1.43) were associated with significantly higher atomoxetine use. In contrast non-Caucasian race was associated with decreased atomoxetine use (OR between 0.56 to 0.69). Diagnosis of ADHD with hyperactivity decreased the odds of atomoxetine initiation (0.85 OR, 95% CI, 0.82-0.88). Per calendar year, the propensity of atomoxetine use continuously decreased to OR = 0.34 (95% CI 0.33-0.35) for 2003 versus 2006.

Conclusions: Propensity of treatment initiation with atomoxetine compared to CNS stimulants decreased over time, possibly associated with safety concerns. Substance use disorder and tic disorder were associated with increased odds of atomoxetine initiation, in concordance with current guidelines. However, increasing age, ADHD with hyperactivity, disability and non-Caucasian race was associated with significant lower odds of receiving atomoxetine.

389. Prevalence and Determinants of ADHD Medication of Children and Adolescents in Germany – Results of the KiGGS Study

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Background: Prescriptional data of Statuary Health Insurances in Germany indicates an increase of pharmacotherapy of ADHD in children and adolescents. There is no population based information about user prevalence and user profiles.

Objectives: To investigate prevalence and spectrum of ADHD medication and its associations with socioeconomic status, health-related behaviour and living conditions.

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Methods: Design: Observational cross-sectional study. Setting: Germany. Participants: Representative population-based sample of non-institutionalized boys and girls aged between 0 and 17 years (n = 17,461), examined between 2003 and 2006. Main outcome measure: Prevalence and spectrum of ADHD medication (ATC code N04BA06) measured by standardized computer-assisted personal interview on drug use. Statistics: Analyses were performed using SPSS statistical software (release 18.0). In order to adjust for sample clustering effects, the SPSS complex samples module was used.

Results: The overall prevalence of ADHD medication was 0.9% (95% CI 0.7–1.1). Boys used these drugs (1.5%, 95% CI 1.2–1.8) five times more than girls 0.3% (0.2–0.5%). The highest prevalence rates were for boys aged 7–10 years (2.8%) and 11–13 (2.7%). Boys from families with no immigration background used ADHD medication almost six times as frequently as boys with an immigration background (1.7% vs. 0.3%). Multivariate analysis showed boys (OR 5.23, 95% CI 3.16–8.65), 11- to 13-year-olds (2.02, 1.17–3.49), children in large cities (2.08, 1.12–3.89) and children with no immigration background (3.09, 1.36–7.01) being more likely to use ADHD medication.

Conclusions: Results show prevalence rates of ADHD medication use for the German child population that are considerably lower than published prevalence rates from the United State, but comparable with those of western European and Scandinavian countries. Lower use rates in rural vs. urban regions may point to differential health care access. The inverse association of ADHD medication use with immigration status suggests potentially restricted access to healthcare services for immigrants or may reflect culture-specific differences in attitudes towards symptoms of ADHD.

390. The *SLCO1B1* c.521T > C Polymorphism and the Risk of Adverse Reactions during Simvastatin and Atorvastatin Therapy

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Background: Simvastatin and atorvastatin are substrates for the OATP1B1 transporter, encoded by the *SLCO1B1* gene. The rs4149056 c.521T > C polymorphism in this gene is associated with statin plasma levels and, in simvastatin users, with the risk of adverse reactions.

Objectives: The objective was to investigate whether the c.521T > C polymorphism in the *SLCO1B1* gene modifies the risk of dose decreases or switches to other cholesterol lowering drugs during simvastatin and atorvastatin therapy, as proxy indicators for adverse reactions. We stratified analyses by sex, age and starting dose to investigate whether they are risk factors for the occurrence of adverse reactions during statin therapy.

Methods: We identified 1,939 incident simvastatin and atorvastatin users in the Rotterdam Study, a prospective population-based cohort study of people ≥55 years of age. Follow-up started at the date of first prescription of simvastatin or atorvastatin. Participants were followed until the occurrence of a dose decrease or switch to another cholesterol lowering therapy, the end of the last prescription for simvastatin or atorvastatin, or until the end of 3 years of continuous use. Association between the *SLCO1B1* c.521T > C polymorphism and the time to the events was studied using Cox proportional hazards analysis.

Results: Simvastatin users with the rs4149056 CC variant genotype had a significantly higher risk of an adverse reaction than users with the TT genotype (HR 1.74, 95% CI 1.05–2.88). Female gender, age below 70 years, and a low starting dose were risk factors for this association. In atorvastatin users with a starting dose of more than 1.00 defined daily dosage (DDD), the risk of an adverse reaction was higher in users with the TC or CC genotype than in users with the TT genotype (HR 3.26, 95% CI 1.47–7.25).

Conclusions: In simvastatin users, we confirmed the previously described association between the c.521T > C polymorphism and adverse reactions, and provided risk factors for this association. In atorvastatin users, an association was found in users with a starting dose above the daily recommended dose.

391. CYP2C9 Variants and Risk of Gastrointestinal Bleeding Associated with NSAID Use: A Case-Control Study

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Background: Gastrointestinal hemorrhages (GIHs) associated with nonsteroidal anti-inflammatory drugs (NSAIDs) consumption are one of the most frequent and severe adverse drug reactions. The enzyme CYP2C9 metabolizes most NSAIDs, and the gene encoding the synthesis of this enzyme, has slow metabolizing variants that could increase the risk of GIH among NSAID users.

Objectives: To ascertain whether the presence of the *CYP2C9*2* and/or *CYP2C9*3* variant might increase the risk of suffering from NSAID-related GIHs.

Methods: A multicenter incident case-control study was conducted at five hospitals in south-west Europe: cases were persons with GIH diagnosed by endoscopy, and controls were candidates for surgery of non-painful processes. The NSAID exposure was quantified by calculating the mean defined daily dose (DDD) consumed. The assessment of the Hardy-Weinberg equilibrium was carried out in both *CYP2C9*2* and *CYP2C9*3* variants. A multivariate analysis was performed to assess the effect of NSAID use on increased risk of suffering from GIHs, taking the presence of *CYP2C9*2* and *CYP2C9*3* variants into account and non-NSAID users with wild-type genotypes as reference.

Results: A total of 581 cases and 1358 controls proved eligible for study; 40.2% of cases and 59.1% of controls carried either or both of the variants studied. Allele analysis showed that the ORs of GIH associated with the CYP2C9*2 and wild type variants were very similar [7.12 (95% CI 2.34–21.73) and 6.87 (4.02–11.72) respectively] and lower than those for the *CYP2C9*3* variant [OR = 19.85 (7.42–53.07)] for mean defined daily doses of NSAIDs metabolised by CYP2C9 exceeding 0.25. Grouping genotypes into carriers and non-carriers of the *CYP2C9*3* variant yielded ORs of 18.89 (5.79–61.64) for carriers and 7.05 (3.95–12.58) for non-carriers.

Conclusions: Our findings indicate a genetic predisposition among *CYP2C9*3* carriers to suffer from NSAID-related GIHs. These results may have wide-ranging clinical implications, since 14% of the population of European origin carries this variant.

392. Lack of Association between *SLCO1B1* Polymorphisms and Clinical Myalgia Following Rosuvastatin Therapy

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Background: Carriers of the rs4363657 C allele and rs4149056 C allele in *SLCO1B1*, the gene that encodes the organic anion-transporting polypeptide OATP1B1, a regulator of hepatic uptake of statin, have an increased incidence of myopathic complaints when taking simvastatin. Whether rosuvastatin has a similar effect is uncertain.

Objectives: To help understand if genetic variation in *SLCO1B1* contributes to increased risk of myopathic complaints following rosuvastatin therapy.

Methods: In the recently completed JUPITER trial, men and women without prior cardiovascular disease or diabetes who had baseline LDL-C < 130 mg/dL and high sensitivity C-reactive protein 2 mg/L were randomly allocated to rosuvastatin 20 mg daily or to placebo and followed for first major cardiovascular events, as well as for adverse effects. We evaluated the effect of polymorphisms rs4363657 and rs4149056 in *SLCO1B1* on clinically reported myalgia in this primary prevention trial.

Results: Overall, among 4,404 Caucasian trial participants randomly allocated to rosuvastatin, clinically reported myalgia occurred with a rate of 4.1 events per 100 person-years as compared to a rate of 3.7 events per 100 person-years among 4,378 Caucasian trial participants allocated to placebo (HR 1.13, 95% CI 0.98–1.30). Among those allocated to rosuvastatin, there were no differences in rate of myalgia among carriers of the rs4363657 C allele (HR 0.95, 95% CI 0.79–1.14 per allele) or the rs4149056 C allele (HR 0.95, 95% CI 0.79–1.15 per allele) when compared to non-carriers. Similar null data were observed when the definition of myalgia was broadened to include any complaint of muscle weakness, stiffness, or pain. None of the three participants in the rosuvastatin group or the three participants in the placebo group with frank myopathy were carriers of either polymorphism.

Conclusions: In contrast to simvastatin, there appears to be no increased risk of myalgia among users of rosuvastatin who carry the rs4363657 C or the rs4149056 C allele in *SLC01B1*, and consequently no clinical utility to evaluat-

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ing genetic polymorphism in *SLCO1B1* among individuals being treated with rosuvastatin.

393. Vascular Endothelial Growth Factor (*VEGF*) Pathway Polymorphisms and Esophageal Cancer Outcome

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Background: Angiogenesis is a host pathway involved with cancer proliferation and progression. Therapies targeting this pathway include Bevacizumab. However, to understand drug pharmacogenetics properly, a greater understanding of baseline prognostic biomarkers in this pathway is required. Polymorphisms in the VEGF pathway have been previously implicated in cancer risk, progression, survival and response to therapy.

Objectives: We comprehensively evaluated the *VEGF* polymorphic pathway and their prognostic role in esophageal cancer patients not treated with an anti-angiogeneic drug.

Methods: In 314 esophageal cancer patients of all stages, histological subtypes, and treatment plans, 68 different polymorphisms (22 *KDR*, 13 *VEGFA*, 33 *FLT1*) were selected through tagging and assessment of function. Genotyping was conducted using the Illumina Custom GoldenGate Genotyping Panel. Cox proportional hazards models, adjusted for important clinical prognostic factors, were created and used to determine association of polymorphisms with the clinical outcomes of overall survival (OS) and progression free survival (PFS). Adjusted hazard ratio (aHR) and p values were calculated using SAS.

Results: Among our 314 patients, 84% were male, the overall mean age was 65 years, 73% were adenocarcinomas, 52% were locally advanced tumors and the median OS was 2 years. *KDR* (rs17709898) and *KDR* (rs2219471) were both found to be significantly associated with PFS (aHR = 0.73, 95% CI: 0.59–0.89; p = 0.001, and aHR = 0.71, 95% CI: 0.57–0.90; p = 0.003, respectively). Their corresponding associations with OS were aHR = 0.76, 95% CI: 0.61–0.95; p = 0.01, and aHR = 0.76, 95% CI: 0.60–0.98; p = 0.03, respectively. None of the *VEGFA* or *FLT* polymorphisms were found significantly associated with either outcome.

Conclusions: *KDR* polymorphisms may serve as prognostic markers in esophageal cancer patients helping to stratify patients into different prognostic groups which can impact their aggressiveness/selection of therapy and follow-up frequency. Future studies should investigate whether these polymorphisms can also serve as predictive markers of anti-angiogenic therapy.

394. Extraction of Hepatitis C Genotype from Clinical Notes for Patients Missing a Veterans Affairs Lab-Confirmed Genotype

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Background: A patient's hepatitis C genotype is an important factor in determining treatment duration, but may be missing from an institution's laboratory data if it is drawn elsewhere or not entered into the database. Providers note the results in text notes during treatment, so retrospective studies can extract the missing data from the notes using NLP and avoid patient exclusion due to incomplete data.

Objectives: In a study of early discontinuation among veterans treated for HCV in the VA, 21.16% were missing genotype values in their laboratory data. The study required HCV genotype values to determine if the recommended treatment was 24 weeks (genotypes 2 or 3) or 48 weeks (genotypes 1 or 4). The actual days treated was compared to recommended treatment to determine early discontinuation. Natural language processing was utilized to extract mentions of genotype from the text notes.

Methods: Text notes were obtained for patients treated for HCV in the VA but missing laboratory genotype data. Review of the notes identified common sections and phrases in which genotype information was noted by the provider. An NLP system using regular expressions and rules was developed to locate and extract these genotype mentions.

Results: Twenty-two thousand two hundred fourty-nine patients were treated for HCV within the study period and 4,709 (21.16% of the cohort) were missing genotype data. The NLP system identified genotype values for 4,092 (86.9% of those missing data), reducing participant drop out from 21.16% to 2.77%. 93.9% of patient records had more than one genotype mention, 49.7% had more than 10 mentions, and 21.9% had more than 20 mentions.

Conclusions: The NLP extraction of genotype data was successful in reducing missing data for this study from 21.16% to 2.77%, and increased the cohort size from 17,540 to 21,632 patients. This study shows NLP can be a fast and effective method to extract critical information that is missing in structured data sources, but is recorded in text notes.

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395. The Effect of Omeprazole and Esomeprazole on the Maintenance Dose of Phenprocoumon

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Background: Vitamin K antagonists like phenprocoumon are sensitive to interactions with other drugs, including drugs metabolized by cytochrome P450 enzymes. Omeprazole and esomeprazole are frequently used drugs metabolized by these enzymes.

Objectives: The aim of this study was to determine whether omeprazole and esomeprazole affect the mean stable phenprocoumon maintenance dose and whether inclusion of these proton pump inhibitors can improve the predictive value of a pre-existing dosing algorithm.

Methods: Data from the pre-EU-PACT trial were used to investigate the stable phenprocoumon maintenance dose (mg/day) in omeprazole and esomeprazole users compared to non-users. In this retrospective cohort study 624 patients using phenprocoumon with a target INR of 2.0–3.5 were included from an anticoagulant clinic in the Netherlands. Multiple regression analysis was conducted in which we included a term for omeprazole or esomeprazole use to optimalize the genotype-guided algorithm that was developed earlier.

Results: A stable maintenance dose was reached within one year by 597 patients. Of these, 533 patients did not use omeprazole or esomeprazole. fourty-six patients used omeprazole and 18 patients used esomeprazole. On average, non-users required 2.27 (SD: 0.90) mg phenprocoumon per day. The dosage was significantly lower in both omeprazole users (1.78 mg/day, SD: 0.73, 95% CI of the difference: 0.22–0.75) and esomeprazole users (1.88 mg/day, SD: 0.52, 95% CI of the difference: 0.12–0.66). Omeprazole or esomeprazole use significantly influenced the phenprocoumon maintenance dose ($p = 0.002$) in a genotype (*CYP2C9* and *VKORC1)*-guided dosing algorithm. The inclusion of this term improved the predictive value of the algorithm by 0.8% to a predictive value of 56.7%.

Conclusions: Omeprazole and esomeprazole significantly lower the phenprocoumon maintenance dose and including a term for omeprazole/esomeprazole use in a phenprocoumon dosing algorithm improves the accuracy of this algorithm.

396. New Psychiatric Diagnoses and Medication Use after Intensive Care: A Danish Nationwide Cohort Study

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Background: Small cohort studies indicate an increased risk of psychiatric illness after critical illness, but population-based data are lacking.

Objectives: To examine one-year risk of first-time psychiatric illness among patients surviving a medical intensive care unit (ICU) admission requiring mechanical ventilation.

Methods: We conducted this nationwide cohort study in Denmark using individual-level linkage of medical databases. We included all Danish ICU patients treated with mechanical ventilation while admitted to ICUs in Denmark in 2006–2008 who had no surgery on the day before or the day of ICU admission. We sampled a hospital comparison cohort of patients admitted to the same referring wards as the ICU patients within ±180 days of the corresponding ICU patient's admission date.

We described the proportion with psychiatric diagnoses or medication use before admission and computed one-year post-discharge risk of filling a first-time prescription for psychiatric medications and of a first psychiatric in- or outpatient diagnosis, accounting for the competing risk of death. We used Cox regression to compute hazard ratios (HRs) for these outcomes, comparing ICU patients with the hospital cohort, adjusted for potential confounders.

Results: We identified 24,179 mechanically ventilated medical ICU patients of whom 48.7% had psychiatric medication and 6.2% had psychiatric diagnosis within 5 years before ICU admission. These proportions were similar in the hospital cohort (48.8% and 5.4%). Among the 9,912 hospital survivors without psychiatric diagnoses or medication, the 1-year risk of filling a psychiatric medication prescription was 25.8% compared with 15.5% in the hospital cohort, corresponding to an adjusted HR of 1.87 (95% CI: 1.74–2.01). The HRs were very similar according to types of psychiatric medication. The one-year risk of a psychiatric hospital diagnosis was 1.1% for the ICU patients (adjusted HR = 2.15, 95% CI: 1.52–3.04).

Conclusions: We found a roughly two-fold increased risk of a new psychiatric diagnosis or psychiatric medication

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use in the first year after an ICU admission for severe critical illness compared with other hospitalized patients.

397. Access, Benefit Design, and Antipsychotic Drugs in the Medicare Part D Program

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Background: Antipsychotics receive formulary protection under Medicare Part D; however, they are subject to standard cost-sharing requirements, including the coverage gap. Beneficiaries with schizophrenia or bipolar disorder receiving antipsychotics may be at high risk of experiencing adverse effects associated with cost-related non-adherence.

Objectives: We examined the impact of Part D cost-sharing on antipsychotic spending, adherence, and clinical events among beneficiaries with schizophrenia or bipolar disorder.

Methods: The study includes Medicare Advantage beneficiaries receiving antipsychotics in 2006 with schizophrenia or bipolar disorder diagnoses in 2006–2007 (N = 7,352); 49.6% had a gap in 2007, the remainder did not due to low income subsidies. We used difference-in-difference fixed effects models to examine within-person changes in total and out-of-pocket spending and adherence (proportion of days covered, PDC) during vs. before the gap for subjects with gaps vs. without. For subjects without gaps, we used the gap threshold ($2400). We used proportional hazard models to examine ED and hospital events, adjusting for gender, age, risk score, and reaching the gap threshold.

Results: Among beneficiaries with coverage gaps, 43% (schizophrenia) and 54% (bipolar disorder) entered it in 2007. For beneficiaries with gaps vs. without, monthly antipsychotic spending decreased (e.g., schizophrenia: -$126 [-$142, -$112]) and out-of-pocket spending increased (e.g., schizophrenia: $112 [$106, $117]) post vs. pre-gap. Adherence (PDC) similarly decreased after gap entry (e.g., schizophrenia: -17.2 percentage points[-18.7, -15.7]). Hospitalizations and ED visits rates also increased after gap entry (e.g., schizophrenia: HR = 1.3[1.1, 1.5] and bipolar disorder: HR = 1.5[1.2, 1.7] for all hospitalizations vs. pre-gap).

Conclusions: Out-of-pocket costs increased, and total antipsychotic spending and adherence declined in the gap. Adverse events also increased during the gap. Medicare will phase out the gap by 2020, but beneficiaries will continue to face substantial cost-sharing. Future benefit designs should account for out-of-pocket costs when considering access and align these costs with clinical benefits.

398. Antidepressants and Risk of Discontinuation of Diabetes Medicines

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Background: Compliance with medication regimens for patients with diabetes is crucial to achieve treatment success. Whilst comorbid depression is associated with poor medication adherence in patients with diabetes, little is known about the effect of depression or use of antidepressants on persistence with anti-diabetic medicines.

Objectives: To examine the effect of antidepressant use on persistence with newly initiated oral anti-diabetic medicines in older people.

Methods: A retrospective cohort study was undertaken on administrative claims data from the Australian Government Department Veterans' Affairs, from 1st July 2000 to 30th June 2008 of new users of oral anti-diabetic medicines (metformin or sulfonylurea). Antidepressant medicine use was determined in the six months preceding the index date of the first dispensing of an oral anti-diabetic medicine. The outcome was time to discontinuation of diabetes therapy in those with anti-depressant use compared to those without. Competing risks regression analyses were conducted with adjustment for covariates.

Results: A total of 29,710 new users of metformin or sulfonylurea were identified, with 7,171 (24.2%) dispensed an anti-depressant. Median age was 79.1 years (IQR 75.0–83.4), 60.2% were men, 58% were initiated on metformin and 42% on sulfonylureas. Median duration of anti-diabetic medicines was 1.81 years (95% CI 1.72–1.94) for those who received an antidepressant at the time of diabetes medicine initiation, by comparison to 3.23 years (95% CI 3.10–3.40) for those who did not receive an antidepressant. Competing risk analyses showed a 42% increased likelihood of discontinuation of diabetes medications in persons who received an antidepressant (SHR 1.42, 95% CI 1.37–1.47, $p < 0.0001$).

Conclusions: This large population based study demonstrates that depression may be contributing to non-compliance with medicines for diabetes which may lead to poorer disease control and health outcomes. This highlights the need to provide additional services to support appropriate medicine use in those initiating diabetes medicines with comorbid depression.

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399. Persistence and Dose Escalation in the Use of Anti-Dementia Medication

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Background: In recent years anti-dementia (AD) medications have been widely used with many large studies reporting improvements in cognitive scores, function and behaviour to varying degrees. However, these outcomes can be affected by low persistence and inappropriate dose titration.

Objectives: The aims of the study were to examine: (1) prevalence and predictors of persistence amongst new users of AD medication and (2) changes to dosing post-initiation in the "real world" setting.

Methods: The Irish HSE Primary Care Reimbursement Services (PCRS) pharmacy claims database for 2007–2010 was used to define a retrospective cohort of all those aged ≥70 years, the main beneficiaries of AD medication (donepezil, rivastigmine, galantamine and memantine). New users of therapy were defined as not receiving any AD medication in the previous 12 months. Non-persistence was defined by a refill gap of more than 63 days at 6 months (in those with adequate follow-up). Logistic regression was used to examine predictors of persistence, including age, gender, initiation year and type of agent. Odds ratios (OR) and 95% confidence intervals (Cis) are presented. The rate of dose maximisation over time was also examined.

Results: During the period, 15,549 patients initiated AD medications and had at least 6 months follow-up. Donepezil and memantine were the two most commonly prescribed (n = 13781, 86.6%). Almost one quarter of patients (22%) initiated more than one AD drug during the study period. Persistence with therapy was 66.1% at 6 months. Older age (75+ vs 70–74 years; OR = 0.84, 95% CI 0.75, 0.93) and the prescription of rivastigmine (compared to donepezil; OR = 0.85, 95% CI 0.75, 0.97) was associated with lower persistence. Persistence was higher following more recent drug initiation (2010 vs 2007; OR = 1.23, 95% CI 1.1, 1.38). Of those initiating donepezil, most achieved the maximum dose of 10mg daily (9634, 86%), but only two thirds for ≥2 consecutive months (7305, 65.2%). Similarly for memantine, maximum dose (20mg) was achieved in the majority (4941, 89.7%), but maintained for ≥2 consecutive months in 69.8% of cases.

Conclusions: Despite a significant proportion of patients being prescribed the maximum dose of donepezil and memantine, only two-thirds of patients maintained this maximum dose. Persistence with medication was relatively low, perhaps reflecting drug intolerance or inadequate surveillance of drug compliance in this cohort. As part of our National Dementia Strategy (2013) there is scope to introduce clearer national guidance on prescribing in dementia care.

400. Characteristics and Trends of Low-Dose Second Generation Antipsychotic Use in Two State Medicaid Programs

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**Background: ** AstraZeneca recently settled a $520 billion lawsuit alleging illegal promotion of quetiapine to psychiatrists and other physicians for off-label conditions from 2001 through 2006. As the predominate payer for mental illness in the US, state Medicaid programs have voiced concerns that low-doses of SGA, particularly quetiapine, are prescribed excessively for off-label conditions.

Objectives: The goal of this study was to identify patient characteristics associated with low-dose SGA use and describe low-dose SGA prescribing trends over time.

Methods: We employed a retrospective cohort study of SGA initiators from 2004 through 2008 using administrative claims data from Oregon and Colorado Medicaid. For each initiation, we estimated the maximum daily dose and categorized it as low if it was below established ranges for serious mental illness. Baseline comorbidity and pharmacotherapy were characterized and summarized by dose achieved. A segmented trend analysis was used to determine if rates of low-dose SGA prescribing changed during and following the period of off-label promotion.

Results: A total of 14,287 unique patients initiated a SGA during the study. The most commonly initiated SGA was quetiapine. Bipolar disorder was prevalent in 28% and 17% of Oregon and Colorado users respectively ($p < 0.001$). Schizophrenia was prevalent in 16% and 9% of users in both states ($p < 0.001$) respectively. While 52% of incident SGA users were found to be taking a low dose, 69% of quetiapine users were classified as taking a low dose. In Oregon, the use of low dose SGA significantly declined after the period of off-label promotion (-4.7%, $p = 0.03$) but there was no change in the rate of use (slope) after off-label promotion was discontinued. In contrast, the rate (slope) of low-dose quetiapine use declined in Colorado (-0.25% per month; $p = 0.045$) and Oregon (-0.25% per month; $p = 0.098$) following the off-label promotion period.

Conclusions: While low-dose quetiapine use was common among Medicaid recipients in both Oregon and Colorado, incident use has declined following discontinuation of off-label promotion by AstraZeneca.

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401. Trends in Prevalence of ADHD Drug Treatment in the Netherlands from 2000 until 2010

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Background: ADHD is a major concern since it is one of the most common mental disorders affecting children and adolescents. The prevalence of ADHD has been reported to be increasing in the past decade.

Objectives: To assess the trends in prevalence of ADHD drug use in the Netherlands from 2000 until 2010.

Methods: From the PHARMO database, including amongst others, drug dispensing records of approximately 3.2 million inhabitants in the Netherlands, we selected patients with at least one dispensing of ADHD medication including methylphenidate, dexamphetamine and atomoxetine, between 2000 and 2010. For each calendar year, patients were counted as prevalent ADHD drug users if they received a dispensing for ADHD treatment in the respective calendar year. The number of ADHD drug users in PHARMO was divided by the number of residents in PHARMO and multiplied by the number of inhabitants in the Netherlands, standardized for age and gender. Results were stratified by age groups and gender.

Results: The prevalence of ADHD drug treatment among males was higher than among femals. From 2000 to 2010, the prevalence among children (0–12 years) has increased 2.6-fold in males (from 158 to 410 per 10,000) and 4.5-fold in females (from 27 to 119 per 10,000). The prevalence among adolescents (13–18 years) has increased 4.0-fold in males (170–675 per 10,000) and 7.4-fold in females (27–200 per 10,000). The prevalence among adults (19+ years) has increased 8.2-fold in males (from 8 to 63 per 10,000) and 10.1-fold in females (from 4 to 43 per 10,000).

Conclusions: This study provides a comprehensive overview of trends in prevalence of ADHD drug treatment in the Netherlands. Both in males and females, a continuous increase in prevalence was observed.

402. Orlistat and the Risk of Acute liver Injury: A Self-Controlled Case-Series Study in United Kingdom General Practice Research Database

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Background: In 2009 based on spontaneous reports of serious liver injury the US FDA announced orlistat may be linked to an increased risk of hepatic events. No causal association has been established.

Objectives: To investigate the association between orlistat and the incidence of acute liver injury.

Methods: A self-controlled case-series design using the United Kingdom General Practice Research Database (GPRD) and linked Hospital Episode statistics (HES). People were eligible if they had an incident occurrence of idiopathic acute liver injury with a diagnoses recorded (in GPRD or HES) and were exposed to orlistat at any time in the observation period. If there was evidence of a known cause for liver disease, such as alcoholism, patients were excluded. Observation time for each patient was divided into strata determined by orlistat exposure status (30 day strata) and current age. Within-person rate ratios (with 95% confidence intervals) for liver injury were estimated using conditional poisson regression (Stata 12), comparing exposed with unexposed periods.

Results: In the GPRD, between 1999 and 2010, 94,695 people had received at least one prescription for orlistat, of which 1,741 had an eligible diagnosis recorded. Of these, 408 people fulfilled eligibility criteria for a definite event (including abnormal liver function test results and a referral). We found a higher incidence of events in the first 30 days of exposure, (compared to unexposed) RR 2.27 (95% CI 1.12–4.59) and in the 90 days pre-exposure RR 1.96 (95% CI 1.35–2.85) and no difference between 90 days prior and 90 days post prescribing, RR 0.78 (95% CI 0.42–1.42).

Conclusions: This is the first study we are aware of to explore the risk of liver injury associated with orlistat. We found an increased risk of liver events in the 90 days immediately prior to and post first orlistat prescription, but no difference in risk between the pre and initial exposure periods. This suggests that orlistat may be initiated during a period of time when adverse liver events are more likely due to poor underlying health, but does not suggest the risk increases with initiation of orlistat.

403. Comparative Effectiveness of Linezolid and Vancomycin among a National Cohort of Veterans Affairs (VA) Patients with Methicillin-Resistant *Staphylococcus aureus* (MRSA) Pneumonia

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Background: MRSA is a major cause of pneumonia with limited treatment options. Vancomycin has been considered the standard of care for MRSA pneumonia, however, variability in dosing, susceptibility, and tolerance have driven the need to compare newer agents in real world clinical settings.

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Objectives: To determine the effect of linezolid (LZD), compared to vancomycin (VAN), on clinical outcomes for the treatment of MRSA pneumonia in a national VA cohort.

Methods: We conducted a retrospective cohort study of VA hospital admissions between January 2002 and September 2010 with diagnosis codes for MRSA and pneumonia. Pharmacy records were used to identify initiation of LZD or VAN during the admission, with at least 3 days of therapy. Analyses were carried out in three cohorts: overall, validated (algorithm developed from electronic medical record review in 10% sample), clinical (plus symptoms). Propensity score matched and adjusted Cox proportional hazards regression models quantified the effect of LZD compared to VAN on 30-day mortality (primary), therapy change, hospital discharge, transfer out of intensive care, intubation, 30-day readmission, and 30-day MRSA re-infection.

Results: We identified 5,270 patients meeting our inclusion criteria (328 LZD, 4,942 VAN). While a number of baseline variables differed significantly between the two treatment groups, balance was observed within propensity score quintiles and matched patients (252 pairs). The overall 30-day mortality rate was 20.8% (19.5% LZD, 20.9% VAN, p = 0.56). Time to 30-day mortality did not vary significantly between LZD and VAN (adjusted hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.70–1.17; matched HR 1.05, 95% CI 0.69–1.60). While a significantly decreased rate of therapy change was observed in the LZD group with the adjusted model (HR 0.68, 95% CI 0.48–0.96), this difference was not observed in the matched model (HR 0.66, 95% CI 0.40–1.09). Comparable findings were observed in all 3 cohorts.

Conclusions: Clinical outcomes were similar among those treated with LZD or VAN for MRSA pneumonia in our national VA study.

404. Risk of Venous Thromboembolism among Taiwan Osteoporosis Population: Alendronate vs Raloxifene Users

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Background: Potential linkage of venous thromboembolism (VTE) and raloxifene has been found in clinical trials. The mechanism might come from osteoporosis itself or use of osteoporosis drugs. However, the risk has not been examined in Asian population.

Objectives: To compare the risk of developing VTE among Taiwan osteoporosis population taking alendronate or raloxifene.

Methods: Enrollees in the National Health Insurance Research Database (NHIRD) aged above 50 years who were new users of alendronate or raloxifene between 2003 and 2006 were included in this study. Patients with cancer, Paget's disease, deep vein thrombosis (DVT) and pulmonary embolism (PE) diagnosis were excluded. Eligible patients were then grouped according to their prescriptions (alendronate or raloxifene group), and followed from 1st date they received prescriptions until the occurrence of study outcomes or 2007/12/31, whichever came first. Claims of DVT or PE combined with use of anticoagulation therapy were identified as the study outcomes. We quantified a propensity score for the likelihood of receiving alendronate or raloxifene therapy conditional on covariates, which were known to be related to osteoporosis and study outcomes. Propensity score-matched Cox regression analysis was performed to compare the risk of VTE between alendronate and raloxifene users.

Results: From 2003 to 2006, 19,677 patients were new users of study drugs, and 4,661 patients in the alendronate and raloxifene group were matched by propensity score (c-statistic: 0.698). Baseline covariates distributed evenly across two groups after the matching. And, only 0.13% and 0.15% of patients developed VTE in the alendronate and raloxifene group. Results from Cox regression showed that there was no difference in the risk of VTE between alendronate and raloxifene group (HR, 1.04; 95%CI, 0.35–3.12). Similar results were found across series of sensitivity analyses, including selected patients received higher cumulative dose (≥365 DDDs).

Conclusions: When targeting Taiwan osteoporosis population, the absolute risk of VTE was low and no difference whether patients received alendronate or raloxifene therapy.

405. Quantifying *Staphylococcus aureus* Disease Burden with Clinical Microbiology Culture Data: Attributable Time Trends in a Regional Healthcare System

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Background: *Staphylococcus aureus* is a major public health concern which creates barriers to quality healthcare

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delivery. Assessing epidemiologic trends with clinical data supports quality improvement initiatives and resource allocation for identifying and implementing evidence-based healthcare practices that optimize positive clinical outcomes.

Objectives: To quantify disease burden and attributable time trends of *S. aureus* using a novel database we created of clinical microbiology culture and susceptibility results (methicillin susceptible [MSSA] and resistant [MRSA]) from five acute care facilities of the Veterans Affairs New England Healthcare System.

Methods: Incidence rates of unique admissions with positive clinical cultures were captured from 2003 through 2010. Calculating the time between admission and specimen collection (≤48 hours, >48 hours), *S. aureus* was categorized as community-associated (CA) or healthcare-associated (HA). We analyzed time trends using generalized linear mixed models.

Results: MSSA and MRSA were present in 1.6% and 2.3% of all admissions (n = 186,886), respectively. MSSA incidence remained stable over time, with 17 cases per 1,000 admissions in 2003 and 16 cases per 1,000 in 2010. MRSA incidence decreased from 25 cases per 1,000 admissions in 2003 to 17 cases per 1,000 in 2010, representing a significant 7% decrease per year in the modeled incidence (95% confidence interval [CI] -8% to -5%, $p < 0.0001$). The incidence of both HA-MRSA and CA-MRSA decreased significantly, with modeled yearly percent changes of -11% (95% CI -12% to -8%, $p < 0.0001$) and -2% (95% CI -4% to -1%, $p = 0.04$), respectively. The annualized decrease in incidence was greatest for HA-MRSA bacteremia (-15%, 95% CI -18% to -10%, $p < 0.0001$) and HA-MRSA pneumonia (-12%, 95% CI -14% to -9%, $p < 0.0001$), with similar decreases observed in CA-MRSA. For skin and soft tissue culture sites, CA-MRSA increased 4% per year (95% CI 1% to 8%, $p = 0.007$), while HA-MRSA dropped 7% annually (-11% to -3%, $p = 0.0004$).

Conclusions: While we observed lower rates of MRSA over time, these declines were largely, but not wholly, attributable to decreases in HA-MRSA.

406. The Prevalence of X-Linked Hypohidrotic Ectodermal Dysplasia (XLHED) in Denmark from 1995 to 2010

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Background: X-linked Hypohidrotic Ectodermal Dysplasia (XLHED) is a genetic disease caused by a defect in the EDA gene. The classic manifestations of XLHED are absence of sweat glands, a reduced number of hair follicles, and abnormal teeth. Infants with XLHED are at risk of sudden death due to hyperpyrexia. It has been estimated that XLHED accounts for the majority of all Ectodermal Dysplasia (ED), but no estimate based on clinical data for the prevalence of XLHED has previously been made in a large population.

Objectives: To estimate the prevalence of XLHED in the Danish population from 1995 to 2010.

Methods: We conducted this nationwide cross-sectional study in Denmark (population 5.5 million) in the period 1995–2010. We used the Danish National Registry of Patients and ICD-10 codes to identify individuals with an ED diagnosis or with diagnoses for features associated with XLHED. Using the Central Registration System we were able to link relevant clinical data from the departments of Clinical Genetics, Dermatology, Pediatrics, and Specialized Dentistry Centers. We categorized patients with a positive gene test for XLHED as confirmed cases, patients with an ICD-10 diagnosis for ED as probable cases, and patients with sufficient clinical features as possible cases using a clinical algorithm we designed. We calculated prevalence estimates on the basis of these groups and investigated the medical history for all patients.

Results: We identified 1,224 persons who qualified to further examination. Of these 90 were confirmed cases, 146 probable cases and 988 possible cases. This amounts to an overall prevalence estimate of 21.9 cases per 100,000 persons and 1.6 confirmed cases per 100,000 persons. The clinical feature most frequently present was hypodontia, present in 79% of all cases.

Conclusions: The overall prevalence estimate of XLHED was 21.9 cases per 100,000. The most frequent clinical marker for XLHED was hypodontia.

407. Risk of Incident Cardiovascular Disease Events in Patients with Psoriasis: A Retrospective Cohort Study Using the General Practice Research Database

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Background: In recent years, the link between psoriasis and cardiovascular disease (CVD) risk factors has received great attention, however it is still not fully elucidated whether this association translates in an increased risk of developing CVD.

Objectives: To compare CVD risk factors and the risk of developing selected CVD endpoints (myocardial infarction (MI), stroke, transitory ischaemic attack (TIA), heart failure, unstable angina) between psoriasis and psoriasis-free subjects.

Methods: This was an observational, retrospective, database study in a cohort of 59,255 patients aged 18–79 with

a first-time recorded diagnosis of psoriasis in the UK-based General Practice Research Database (GPRD), identified between Jan 1, 2000 and December 31, 2010 (mean follow-up 4 years). These patients were matched 1:1 with individuals without psoriasis. Cox proportional hazard models were used to estimate hazard ratios (HRs) for the development of each of the CVD outcomes, in psoriasis vs. psoriasis-free patients, adjusting for known confounders of each CVD event.

Results: Psoriasis patients were more likely to be obese (17.5% vs. 14.2%), with a history of type 2 diabetes, hyperlipidemia, hypertension and/or on antihypertensive drugs than psoriasis-free subjects; and more likely to be current smokers and to have a history of alcoholism. The crude incidence rates (IRs) and unadjusted HRs showed increased CVD risk in psoriasis patients; e.g., IRs for MI and stroke were 186.8 (95% confidence intervals CIs 170.5–204.6) and 171.5 (CIs 156.0–188.7) per 100,000 person-years in psoriasis patients vs. 183.2 (CIs 166.8–201.3) and 149.2 (CIs 134.4–165.5) respectively in those psoriasis-free. However, the adjusted HRs did not show a significantly increased risk of developing the CVD events of interest among psoriasis patients.

Conclusions: Although CVD risk factors were more likely to be present in patients with psoriasis than in their counterparts without the disease, no greater risk of CVD was observed in psoriasis patients overall.

408. FarmacoEpiEnRed, a Network for Pharmacoepidemiology in Spain

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Background: Pharmacoepidemiological research has increased exponentially in Spain during the past decades, but there is no network linking research groups. The ICPE/ISPE conference to be held in Barcelona, with a large presence of Spanish Pharmacoepidemiologists is a great opportunity to gather them into a single group. Young epidemiologists aim to make this happen.

Objectives: 1. to describe the main organizations and research groups in Spain, and review their contributions;

2. to discuss the need to create the FarmacoEpiEnRed, a network of Pharmacoepidemiologists and the participating institutions;

3. to discuss how the network will improve scientific collaboration.

Researchers interested in learning about Pharmacoepidemiology in Spain and who would like to participate in the network will benefit from attending this workshop.

Description: An overview of publications by Spanish groups, in national and international journals from 1990 to date. This summary will include number of papers, institution name, and setting, as well as information source used for the study. Presentations by pharmacoepidemiologists working in different institutions: Spanish General Practitioners (GP) Databases, Academia, For-profit/ Non-profit Research Organizations, and Industry to provide an overview of history, experience in the field, and future. Discuss the purpose of FarmacoEpiEnRed, a network of pharmacoepidemiologists that will connect and meet regularly, via social networks (e.g., LinkedIn, Skype, Twitter, Facebook), to discuss specific topics in this field, and invite the public to get involved in it. Workshop participants will be encouraged to contribute to the discussion with questions and ideas. Discuss the idea of creating an ISPE Spanish Chapter within ISPE global organization. Discuss future career perspectives. Other goals, proposed by the workshop attendees, will be discussed.

409. Pharmacoepidemiology: The Essential Discipline in the Provision of Safe and Effective Care for Older Patients with Multimorbidity

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Background: Multimorbidity is common in the older population. Those aged 75 years and older will have at least four chronic conditions, taking on average 12 different medicines, 90% will have at least one-medicine related problem and one in five will be living with a current adverse reaction. The care of these patients is complex, and is further compounded by a lack of evidence-based information to guide clinicians caring for patients with multimorbidity. With the proportion of older people increasing worldwide, it is essential that the evidence base for safe and effective medicine use within the context of multimorbidity is addressed. Pharmacoepidemiology provides a way forward for evidence development in the

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"real-life" setting for this population, in terms of best practice, efficacy and safety of therapeutic management using linked datasets, innovative methodological approaches and data analyses.

Objectives: To provide an overview of the challenges in the therapeutic management of older people with multimorbidity and to discuss methodological considerations for the generation of an evidence base to improve health outcomes. The symposium is intended for researchers, clinicians and policy makers with an interest in medicine use in the older population.

Description: This Drug Utilization SIG-endorsed symposium, will consist of two presentations followed by a panel discussion. A speaker will discuss the issues raised above based on her experience in leading a 5 year program of research on evidence development and implementation to improve health outcomes for older patients with multiple chronic conditions (30 minute). A speaker will discuss routine evidence development and the most appropriate methods to use. He will also bring a clinicians perspective to the discussion of best practice for older people (30 minute). The panel discussion will consider issues raised from the perspectives of researchers, consumers, clinicians, clinical pharmacology and regulatory/policy (30 minute).

410. Automatic Generation of a Case-Detection algorithm for Hepatobiliary Disease Using Machine Learning on Free-Text Electronic Health Records

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Background: In observational studies, defining a case-detection algorithm is an important first step. Case-detection algorithms are usually created manually and often only use structured information in the electronic health record (EHR), such as ICPC and ICD-9 codes. Automatic machine-learning methods can be used to generate case-detection algorithms based on a relatively small set of examples. These methods can also learn from unstructured free-text in EHRs.

Objectives: To generate and validate a case-detection algorithm for hepatobiliary disease by taking advantage of both structured and unstructured information in the EHR, using a machine-learning method.

Methods: A training set of 973 hepatobiliary disease patients was created from the IPCI (Integrated Primary Care Information) database, a Dutch general practitioner database containing EHRs of more than 1 million patients, using a broad automatic search on ICPC codes and hepatobiliary disease-related keywords. The set was manually annotated by two medical doctors. The rule-learning algorithm RIPPER was used on the training set to automatically generate rules for the case-detection algorithm. Performance of the generated rules was evaluated against the manually annotated set.

Results: The automated case-detection algorithm had a positive predictive value (PPV) of 0.87, sensitivity of 0.93, and specificity of 0.72. In total, RIPPER generated 19 rules. Only two of the rules contained ICPC codes, and had an average PPV of 0.81. The remaining rules were based on the unstructured free-text with an average PPV of 0.86. The top five rules had a combined PPV of 0.95.

Conclusions: Our results demonstrate that it is possible to automatically generate case-detection algorithms using machine-learning methods. High PPV of the rules generated from the un-structured text show the added value of using complete EHRs for automatic rule generation for case-detection algorithms.

411. Cross-National or Multi-Database Research Networks: A New Initiative in Asia-Pacific Region and Ongoing Initiatives in Europe and United States

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Background: Cross-national comparisons or multi-database studies of drug use, outcomes, and safety have been ongoing in the United States and Europe for some years. The Asian Pharmacoepidemiology Network (AsPEN) is a new multinational research network using a distributed network model. Its goals include support for multi-database research and facilitation of prompt identification and validation of safety issues in Asia. Although several networks now exist, the initiatives differ slightly in goals and structure and carry tremendous potential for expanding pharmacoepidemiologic research. Valuable lessons have been learned from this type of networking. This symposium will focus on three networks: AsPEN, the European Drug Utilization Cross-National Comparison (CNC), and the Observational Medical Outcome Partnership (OMOP).

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Objectives: To increase awareness and interest in a new research network in Asia and ongoing US and European initiatives and to discuss challenges, opportunities, and intersections of the networks to strengthen pharmacoepidemiologic research worldwide. The symposium will consist of a series of presentations on the current status and potential for AsPEN, CNC, and OMOP, and will be followed by a panel discussion involving speakers, panelists, and symposium attendees.

Description: The symposium will be moderated by BJP, ME, and UB (shown by initials) and feature following presentations and panel discussion (presenters/panelists shown by initials):

1. AsPEN in Asia-Pacific Region.

1a. Overview of AsPEN: Goals, future, and intersections with CNC and OMOP (7 minute by YHK).

1b. Current capability and recent projects in AsPEN: Successes and challenges in past studies (15 minute by KK).

1c. Current status in pharmacoepidemiology research in non-AsPEN countries: Singapore, China, and India (8 minute by WPY).

2. CNC in Europe: Goals, current status, and intersections with AsPEN and OMOP (20 minute by BW).

3. OMOP in US: Goals, current status, and intersections with AsPEN, CNC and other networks (20 minute by PS).

4. Panel discussion on lessons learned and future directions and intersections (20 minute by panelists; all speakers, LR, CYC, and MA).

412. Electronic Healthcare Databases for Pregnancy Research: Panacea or Trojan Horse?

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Background: Drug safety studies in pregnancy typically require large study populations because the outcomes tend to be rare. Administrative healthcare databases are used increasingly in pregnancy research, but the strengths, weaknesses, and pitfalls of this approach are not well understood.

Objectives: To discuss the key methodological and practical issues to consider when using electronic healthcare databases to assess drug safety in pregnancy. Researchers involved in the conduct, evaluation, or interpretation of pregnancy studies will benefit from attending.

Description: Each speaker will present their specific experience with electronic databases, focusing on an important design issue. The symposium will conclude with a critical appraisal of current practice, followed by a moderated discussion.

Identification of pregnancies: The approach used and challenges encountered in identifying pregnancies, and linking mothers with their offspring in the nationwide Medicaid Analytic eXtract (MAX) will be presented.

Study population; validity-precision trade-off: Strict eligibility criteria need to be implemented to ensure a continuous and comprehensive stream of claims throughout the observation period. While such exclusions negatively affect study size, validity should never be sacrificed for precision or "perceived" generalizability of the findings. The effect of "relaxing" eligibility criteria on the validity of the estimated exposure-outcome associations will be illustrated using the MAX.

Timing of exposure windows: Administrative databases typically do not contain information on gestational age or the date of last menstrual period (LMP), yet this date is crucial for the correct determination of the exposure time window. Experiences with and relative performance of different algorithms to approximate the LMP date will be discussed.

Outcome ascertainment: Without access to birth certificates, outcomes in database studies have to be identified using diagnostic and/or procedure codes. The validity of this approach has been questioned. Results of studies validating outcomes against medical records when researchers did/did not have access to birth certificates will be contrasted.

413. Evaluating the Effectiveness of Risk Minimisation Measures in the Context of the New Pharmacovigilance Legislation in the EU

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Background: Assessing the effectiveness of Risk Minimisation Measures (RMM) is crucial for regulatory and public health purposes and is required in the new EU pharmacovigilance legislation. However this assessment demands careful tailoring of research methods to ensure that robust evidence is generated to inform benefit-risk evaluations. For products centrally authorized in the EU, the European Medicines Agency (EMA) and its committees, including the newly created Pharmacovigilance Risk Assessment Committee, coordinate regulatory activities,

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while National Competent Authorities maintain authority upon the implementation of additional RMM, in compliance with national regulations.

Objectives: To share experience, knowledge and expectations across sectors on value and limitations of research methods for evaluating RMM effectiveness, including methodological challenges and feasibility hurdles of implementing surveys in the context of EU requirements.

Target audience: Individuals involved in development and assessment of RMM.

Description: Five panellists will bring the perspective of the EU regulatory network, the pharmaceutical industry, and research organisations. Following a 5 minute introduction to the format and a brief overview of EMA experience on assessment of RMM effectiveness, the symposium will include the following speakers and topics:

1. (Co-Chair, Regulatory Perspective) – Concepts, roles and responsibilities in evaluating RMM effectiveness: The EU regulatory network perspective – 15 minute.
2. (Industry Perspective) – Tools for evaluating the effectiveness of risk minimisation measures: the perspective of the industry – 20 minute.
3. (Research Organization Epidemiologic Perspective) - Methodological considerations for surveys evaluating RMM effectiveness: design and analytic strategies to minimize bias – 15 minute.
4. (Research Organization Survey Design Perspective) – Feasibility considerations, including privacy, ethics committees and sample recruitment – 15 minute.

To conclude, Chair and Co-Chair will lead a general discussion (15–20 minute) with the audience and all panellists.

414. Global Collaborations in Vaccine Safety, Present and Future

Robert T Chen,[1] Jan Bonhoeffer,[2] Patrick Zuber,[3] Miriam Sturkenboom,[4] Claudia Velozzi,[1] Hector Izurieta,[5] Michael Greenberg,[6] Steven Black,[7] Thomas Verstraeten.[8] *[1]Centers for Disease Control and Prevention, Atlanta, United States; [2]Brighton Collaboration Foundation, Basel, Switzerland; [3]World Health Organization, Geneva, Switzerland; [4]Erasmus Medical Center, Rotterdam, Netherlands; [5]Food and Drug Administration, United States; [6]Sanofi Pasteur, Lyon, France; [7]University of Cinncinatti, Cinncinatti, United States; [8]P95, Leuven, Belgium.*

Background: Many opportunities for global collaboration arose/will arise from the monitoring the safety of (1) the H1N1 flu vaccine, and (2) new vaccines against poverty-related diseases (PRD) (e.g., dengue, malaria) in low and middle income countries (LMIC)s.

Objectives: Discuss the challenges and opportunities of global vaccine safety monitoring among stakeholders.

Description:

Moderator: 1. The Global Vaccine Safety Blueprint Project. Millions of doses of vaccines are used in LMIC annually. However, few LMICs have the ability to monitor and assure the safe use of vaccines. The Blueprint provides a strategic plan to start doing so.

2. Lessons from H1N1: Rapid assessment and association studies. Updates on: (1) H1N1 vaccine and narcolepsy studies, and (2) the Global Research in Pediatrics (GRiP) as a platform for follow up collaborative distributed studies.
3. Global H1N1 Guillain-Barré syndrome (GBS) study. A common protocol across continents is feasible!
4. Challenges for vaccine safety surveillance in LMICs from the industry perspective. Vaccine manufacturers can perform post-licensure vaccine safety surveillance in high income countries (HIC). In LMICs, where such infrastructure is not readily available, safety information from HIC is usually relied upon. New vaccines that may be marketed first in LMIC's creates new challenges.
4. Assessing the feasibility of collaborative postlicensure studies in LMIC. The PREVENT (PRogram Enhancing Vaccine Epidemiology Networks and Training) project is a partnership between vaccine safety experts and the INDEPTH Network of health and demographic surveillance sites in LMICs.
5. Innovative use of technology for postlicensure studies in LMIC. Traditional pharmacovigilance systems are non-existent in many LMICs. Modern technologies, however, can be borderless. Internet, mobile (increasingly, smart) phones, and vaccine barcodes can aid cost-efficient vaccine safety monitoring in LMICs.
6. Panel discussion with audience participation.

415. Integrating Methods for Semi-Automated Drug Safety Monitoring of Newly Marketed Medications Using Databases: Illustrations with a Prototype

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Background: When a drug enters the market, prescribers and payors require comparative safety and effectiveness evidence to inform treatment and coverage decisions. Large-scale healthcare databases play an essential role in generating comparative safety information since these data are routinely collected in near real time and can be rapidly analyzed. The presenters have accumulated evidence on how to implement a semi-automated approach to rapid and valid drug safety monitoring of newly-marketed medications using sequential cohort analyses in electronic healthcare data.

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Objectives: The workshop objective is to discuss the issues of a monitoring program of newly marketed drugs using multiple healthcare databases from design to decision making and illustrate the working of a prototype that is compatible with standard software, hardware, and the Mini Sentinel data model.

Description: The focus of this 90-minute workshop will be on illustrating the epidemiologic challenges encountered, the choices that need to be made, and the issues encountered when implementing in a distributed database environment. The focus will be on practical applications using modular programs based on standard software, hardware, and the Mini Sentinel data model. We will illustrate the system mimicking the prospective monitoring of the newly marketed Ketek (vs. azithromycin) on liver toxicity, cerivastatin (vs. pravastatin) on rhabdomyolisis, and rofecoxib (vs. nsNSAIDs) on MI. We present computing times, analytic options, diagnostic tools, and decision-making aids.

Topics covered:

The Epidemiology: Design choices (comparator, risk window, etc). Handling confounding in a semi-automated approach. *Bias amplification, collider bias. Matching (fixed* vs. *flexible ratio)*. Estimation: RD vs. RR, AT vs. ITT

Special epidemiologic issues: Distributed multivariate analysis. Dealing with few users in the early phase (DRS + PS). Computational aspects with practical examples:

1. Program modules.
2. Diagnostics and reporting.

Alerting/decision making: 1. Performance metrics, options, and simulation results.

2. Decision analytic approach to safety monitoring.
3. Commentary.

416. Transparent, Reproducible and Reusable Research in Pharmacoepidemiology

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Background: Epidemiological research has been criticized as being unreliable. Scientific evidence is strengthened when the study procedures of important findings are transparent, open for review, and easily reproduced by different investigators and in various settings. Studies often have common scientific workflows. The development of generalized execution engines, reusing epidemiological software/script program code for specific clinical questions, can serve as a valuable tool for transparent and reproducible research.

Objectives: Learn about standards for transparent, reproducible and reusable research and how it is being applied in pharmacoepidemiolgy.

Description: The focus of the symposium will be transparent, reproducible and reusable research. Principles of reproducible research in the context of the Medication History Estimator will be discussed. In addition, an overview of the IMI-PROTECT WP2: Framework for pharmacoepidemiologic studies and the Observational Medical Outcomes Partnership will be given.

Outline: 1. Principles of reliability (Helga Gardarsdottir): Introduction to basic principles of transparent reproducible and reusable research.

2. Standardization (Huifang Liang): Standardization of data for drug utilization studies. A discussion of steps involved to convert the raw data into the readily usable data, including how to impute certain fields with examples.

3. Demonstration of the Medication History Estimator (MHE) and a description of the VINCI EpiTools (Brian Sauer). The MHE will be presented to demonstrate concepts of transparency, reproducibility and reuse.

4. The IMI-PROTECT project (Olaf Klungel & Robert Reynolds). Experiences with developing, testing and disseminating methodological standards for the design, conduct and analysis of database studies will be discussed.

5. Lessons from the Observational Medical Outcomes Partnership (Patrick Ryan, PhD).

Standardized analytics tools developed by the OMOP community to characterize, visualize, and explore the effects of medical products within a distributed network of observational databases will be presented.

6. Closing summary/discussion.

Chairs: Helga Gardarsdottir & Brian Sauer.

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417. Validate in One Data Source and Apply Results to Another – What Could Possibly Go Wrong? Assumptions behind Addressing Outcome Misclassification in Distributed Data Models

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Background: An increasing number of studies and safety surveillance activities rely on distributed data models, where not all of the contributing data systems have the ability to link to clinical data (e.g., medical records) for outcome confirmation. Obtaining estimates of the positive predictive value (PPV) of outcomes identified on the basis of codes, such as those from health insurers may be feasible within one or a few data sources. However, the generalizability of this PPV for addressing outcome misclassification depends on assumptions.

Objectives: To discuss the application of a PPV for correction of outcome misclassification in relative risk estimates when the PPV has been obtained from a validation study that was sampled from a different population.

Description: We will discuss the general problem of outcome misclassification, with a focus on the potential mismatch between a code in a database and a patient's actual diagnosis. Using a specific example from a completed study, this symposium will include three presentations:

1. An introduction to the problem and a standard approach for correcting relative risk estimates for outcome misclassification. Potential limitations to the standard approach will be discussed.
2. A description of extensions of the existing methods to account for differences between the validation sample and the target population using an example where PPV from a single data source was applied within risk factor strata to account for differences in the study populations across data sources.
3. An exploration of refinements that involve the application of disease risk scores. The discussion will also address outcome misclassification when studying treatment effect heterogeneity, with applications of the same methods within a single database.

418. Is Primary Care Ready for Pharmacogenomics? A Feasibility Study of Warfarin Pharmacogenomic Testing in a Family Medicine Clinic

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Background: One in four primary care patients take a medication that commonly causes adverse effects due to genetic variability in drug metabolism . Warfarin (anticoagulant) is an example of this. While pharmacogenomic testing (PGx) to predict optimal warfarin dosing has been established in specialist settings, this has yet to be done in the primary care and there are some concerns about feasibility.

Objectives: To determine if PGx test results can be returned to family physicians in time to potentially modify warfarin dosage.

Methods: This prospective cohort study was conducted at the Family Medicine Clinic at the Queen Elizabeth Health Complex and the Montreal Heart Institute Pharmacogenomics Centre in Montreal, Canada. All family physicians at the clinic and clinic patients receiving warfarin treatment and monitoring were invited to participate. A bioinformatics infrastructure was built between the clinic electronic medical record (EMR) and the genome lab using a validated PGx algorithm. The primary outcome was the time elapsed between ordering the genomic test and result delivery into the EMR with a target of 24 hours (average time to receive INR results). Secondary outcomes included concerns expressed by clinic staff and patients and utility of test results. Descriptive statistics were calculated.

Results: Half of the 30 eligible patients participated in the pilot. The average total elapsed time was 46 hour 37 minute (SD 31 hour 27 m). Mean delivery time to transfer samples from the clinic to the genome lab was 10 hour 2 m (SD 9 hour 17 m) and processing time was 36 hour 35 m (SD 26 hour 52). Two samples had elapsed times of 5 days due to mechanical issues in analysis. Almost half of the results were returned in 24 hours (47%) and another third between 24 and 48 hours (33%). All physicians and nurses within the clinic participated in the study. Patients expressed no concerns with the genomic screening. The clinical algorithm was problematic as it produced dose adjustment recommendations that were too small.

Conclusions: PGx testing for warfarin is feasible in a family practice clinic although improvements need to be made to clinical decision support tools.

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419. Genetic Variants Are Not Associated with Increased Time to Maintenance Dose in Patients Initiating Warfarin Therapy

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Background: Patients starting warfarin therapy will often undergo a lengthy dose titration phase, during which time they are at very high risk of bleeding and thrombosis. While genetic variants can predict a patient's ultimate maintenance dose, it is unclear whether they are associated with a prolonged initial dose titration phase.

Objectives: To determine whether genetic variants and clinical factors are associated with increased time to maintenance dose (TTM) in patients initiating warfarin therapy.

Methods: We used data from IN-RANGE, a prospective cohort study of warfarin patients at three specialized anticoagulation clinics (n = 390). All patients initiating warfarin with a target INR of 2–3 were eligible. Main exposures were variants in *CYP2C9*, *VKORC1*, and *APOE*. Cox proportional hazard models were fitted to assess the association between the genetic variants under study and time from warfarin initiation to maintenance dose in days, with appropriate adjustment for the potential confounders of age, sex, race, BMI, previous warfarin use, insurance status, and frequency of INR visits. The effect of warfarin adherence, measured via micro-electronic monitoring systems (MEMS), was assessed in a secondary subgroup analysis (n = 197).

Results: Seventy-seven per cent of subjects achieved maintenance dose (median TTM = 58 days). None of the genetic variants tested were significantly associated with TTM in either univariable or multivariable analyses (all $p > 0.05$). Frequency of INR visits was the only covariate with a clinically meaningful association with TTM (HR = 5.8 per two visit increase every 4 weeks; 95% CI 4.2, 8.1). In a secondary subgroup analysis, better adherence was associated with faster TTM (HR = 1.4 per 20% increase in adherent days; 95% CI 1.1, 1.8), and the genetic factors remained non-significant.

Conclusions: The genetic variants tested do not appear to be associated with an increase in TTM; instead, behavioral and clinical factors seem more important. These results suggest that pharmacogenetic warfarin dosing strategies may not be able to improve clinical outcomes by decreasing TTM. Ongoing randomized clinical trials will be able to formally test this conclusion.

420. Genetic Variation in GATA-4 Might Affect the Coumarin Maintenance Dose

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Background: It has been shown that the liver-specific transcription factor GATA-4 is involved in the transcriptional regulation of *CYP2C9*. Therefore, it is hypothesized that genetic variations in GATA-4 might play a role in the inter-individual variability in coumarin dose response.

Objectives: To investigate whether the phenprocoumon and acenocoumarol maintenance dose is influenced by genetic variations in *GATA-4*.

Methods: The Pre-EU-PACT database was used, which contains information about 624 phenprocoumon users and 471 acenocoumarol users. Residual INR blood samples were used to genotype *GATA-4*. The influence of variations in *GATA-4* on the phenprocoumon and acenocoumarol maintenance dose was investigated by performing an ANOVA trend analysis. We stratified for *CYP2C9* genotypes. Results of the best explaining SNP for acenocoumarol were validated in the Rotterdam Study. This prospective population-based cohort study among approximately 15,000 persons was designed to investigate different diseases in a population aged over 45 years, including cardiovascular diseases. Complete data was available for 1,265 acenocoumarol users. For phenprocoumon no replication study was available.

Results: Significant effects on the acenocoumarol maintenance dose were found for haplotypes GG and AG in haploblock four and for haplotype GG in haploblock 5&6. These effects were also observed for three SNPs that were part of these haplotypes. The largest dose differences were found for rs3735814 (haploblock 4) in patients being wild type for *CYP2C9*. The mean dosages decreased from 2.92 mg/day for the *GATA-4* wild type patients to 2.65 mg/day for the patients carrying 1 *GATA-4* variant allele to 2.37 mg/day for patients carrying 2 *GATA-4* variant alleles (p = 0.004). Results for rs3735814 could not

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be replicated in the Rotterdam Study cohort. For phenprocoumon, no significant effects were observed.

Conclusions: Genetic variations in GATA-4 appeared to influence the acenocoumarol maintenance dose in the Pre-EU-PACT study. However this could not be replicated in the Rotterdam Study. No significant association was found for the phenprocoumon maintenance dose.

421. Effect of Genetic Variation in the *ABCB1* Gene on Switching, Discontinuation, and Dosage of Antidepressant Therapy: Results from the Rotterdam Study

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Background: P-Glycoprotein (P-gp), encoded by the *ABCB1* gene, is a protein which operates as a multi-drug efflux pump and is widely expressed throughout the body, including the blood-brain-barrier. Functional polymorphisms in P-gp are associated with an increased risk of developing adverse drug reactions during antidepressant therapy, the most intensively studied being 1236C > T, 2677T > A and 3435C > T.

Objectives: This study aimed to assess the association between *ABCB1* genetic polymorphisms and switching and discontinuation of antidepressant therapy within 45 days after starting therapy, and with prescribed dosages in a large population based study.

Methods: We included 1,257 participants from the Rotterdam Study who started antidepressant drug therapy between April 1, 1991 and December 31, 2007, and from whom data on *ABCB1* 1236C > T, 2677G > T/A, and 3435C > T genotypes were available. The association between *ABCB1* genotypes and haplotypes and switching and discontinuation was modeled using logistic regression analyses. In addition, prescribed antidepressant dosage was compared between haplotypes for Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressant (TCAs) drugs separately.

Results: In a model adjusted for age and gender, carriers of the T-T-T haplotype, as compared to C-G-C homozygous carriers, had an increased risk of switching (OR, 95% CI: 4.22, 1.30–13.7) and heterozygous carriers had an increased risk of discontinuation (OR, 95% CI: 1.53, 1.08–2.16). Explained variance was 10.4% for switching and 2.5% for discontinuation. In contrast, no overall difference between the different haplotype carriers was observed in the prescribed dosages of both SSRIs and TCAs.

Conclusions: In summary, this study showed that genetic variation in the *ABCB1* gene was associated with an increased risk of switching and discontinuation of antidepressant therapy, although the explained variance was still low.

422. Analyses of the Effect of Tobacco Smoking on Physiological Measures

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Background: In order for the United States FDA to make evidence-based decisions regarding regulation of tobacco products, there is a need to validate biomarkers which can be linked to early onset of tobacco-caused diseases.

Objectives: The goal is to examine the relationship between physiological measures and smoking status using data from the National Health and Nutrition Examination Survey 2009–2010.

Methods: We examined the relationship between smoking status (established smoker [≥10 cigarettes/day for ≥5 years], and non-smoker [< 100 cigarettes lifetime]) and biomarkers of physiological health: hemoglobin, white blood cells, lymphocytes, monocytes, mean cell volume, and the ratio FEV1/ FVC. The study comprised 2,772 subjects from the NHANES 2009–2010 survey who participated in laboratory screening (504 established smokers and 2,268 non-smokers). For each biomarker, age-specific quartiles were determined. We summed the subject's quartile numbers for each of the six biomarkers and evaluated association between the combined biomarkers and smoking status using polytomus logistic regression. All biomarkers were examined with respect to age, gender, race, and health insurance status.

Results: Estimated mean levels of hemoglobin, white blood cell count, mean cell volume, FEV1/FVC, lymphocyte and monocyte numbers were significantly different between smokers and non-smokers in all age groups ($p < 0.05$). After adjusting for age, race, gender, and insurance status, the combined biomarkers were significantly higher in established smokers than in non-smokers (OR 1.97, 95% confidence interval (CI) 1.85–2.09). The concordance index C increased from 0.6 (95%CI 0.59–0.62) to 0.67 (95%CI 0.66–0.68) when smoking status was added to the model ($p < 0.001$). The results were similar when biomarkers were evaluated individually.

Conclusions: The six biomarkers examined were associated with smoking status, but additional health factors that may affect these biomarkers were not assessed. Results highlight that smoking is associated with markers for decreased health status. Prospective observational longitudinal studies to evaluate how changes in tobacco use affect health over time are needed.

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423. Genetic Polymorphisms and the Risk of New-Onset Diabetes after Transplantation: A Systematic Review and Meta-Analysis

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Background: New-onset diabetes after transplantation (NODAT) is a major metabolic complication of organ transplantation, which is associated with the use of calcineurin inhibitors (cyclosporine and tacrolimus) as immunosuppressants. Accumulating data also suggest that NODAT development may be associated with specific genetic variants.

Objectives: To summarize published evidence from observational studies on the association between various genetic polymorphisms and the risk of NODAT development.

Methods: A systematic search was performed, without language restriction, in PubMed and Scopus databases from their inception to December 2011. For each study, crude odds ratio (OR) and 95% confidence interval (CI) were calculated to estimate NODAT risk with each investigated genetic polymorphism based on the allele contrast model. Random-effects meta-analyses were conducted using Stata/SE software (version 12.0) to pool results for each association between a polymorphism and NODAT with at least two separate studies. Study quality was assessed using an adapted 10-point scoring system.

Results: Twenty-five eligible genetic association studies, assessing 88 polymorphisms, were identified from 629 citations. All studies were conducted on renal transplant recipients. The mean study quality score was 5.2 (range: 3.0–8.9). Out of 22 polymorphisms that were included in meta-analyses, six specific polymorphisms were associated with an increased risk of NODAT in the allele contrast model: SLC30A8 rs13266634 (C vs. T: pooled OR, 1.29 (95% CI, 1.01–1.64); three studies), KCNQ1 rs2237892 (C vs. T: pooled OR, 1.42 (1.09–1.85); two studies), HHEX rs5015480 (C vs. T: pooled OR, 1.51 (1.14–2.01); tw studies), CDKAL1 rs16946398 (C vs. A: pooled OR, 1.42 (1.11–1.83); 2 studies), KCNJ11 rs5219 (T vs. C: pooled OR, 1.40 (1.04–1.89); 2 studies) and ADIPOQ rs2241766 (G vs. T: pooled OR, 1.26 (1.01–1.57); 2 studies).

Conclusions: The risk alleles of SLC30A8 rs13266634, KCNQ1 rs2237892, HHEX rs5015480, CDKAL1 rs16946398, KCNJ11 rs5219 and ADIPOQ rs2241766 were found to increase the risk of NODAT development among renal transplant recipients. These results were, however, based on a very small number of studies. More studies are needed for further independent replication of these findings.

424. Factors Influencing the Adoption of Personalized Genomic Diagnostics in Breast Cancer: A Survey of Oncologists

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Background: The gene expression profiling assay, Oncotype DX® is used to predict the likelihood of breast cancer recurrence and the patients most likely to benefit from adjuvant chemotherapy.

Objectives: The objective of this study was to determine the association between specific characteristics of Oncotype DX® and oncologists' intention to use Oncotype DX® to make treatment decisions for breast cancer patients.

Methods: An online survey of a nationally representative panel of oncologists treating breast cancer was conducted. A questionnaire was designed to study physicians' intentions to use Oncotype DX® and evaluate physicians' perceptions of specific characteristics of Oncotype DX® and how these might either facilitate or serve as a barrier to using Oncotype DX® for making treatment decisions for breast cancer patients. Linear regression analysis was performed to establish the association between physicians' perceptions and intentions to use Oncotype DX®.

Results: A total of 119 completed surveys were received giving a response rate of 51.11%. Of the Oncotype DX® test characteristics evaluated, "validity of the test" ($p = 0.006$) and "use of Oncotype DX® by fellow Oncologists" ($p = 0.0068$) were significantly associated with oncologists' use of Oncotype DX® Oncologists' intention to use Oncotype DX® increased consistently with their perceived usefulness of Oncotype DX® ($\beta = 0.222$).Insurance status of the patients was also significantly associated with physicians' use of Oncotype DX® ($p = 0.008$).

Conclusions: Several characteristics related to Oncotype DX® impact oncologists' intention to use Oncotype DX in the clinical setting to make treatment decisions for breast cancer patients. This study has implications for knowledge translation efforts related to novel personalized genomic medicine applications.

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425. Challenges in Screening Rare Diseases: The ZOOM Experience

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Background: Niemann-Pick disease type C (NP-C) is an inherited lysosomal storage disorder with an incidence of 1:120,000 live births. This is likely to be an underestimate, as most patients experience a considerable diagnostic delay and adult patients may remain misdiagnosed as they present with nonspecific psychiatric symptoms. A genetic screening study showed an increased proportion of NP-C cases in an adult psychiatric population.

Objectives: An international genetic screening study (ZOOM) was designed to evaluate the prevalence of NP-C in adult patients with psychosis or early-onset progressive cognitive decline. Here we describe the challenges we faced in study conduct and interpretation of results.

Methods: Due to the heterogeneous nature of the disease, a multidisciplinary scientific committee has been set up with NP-C experts: geneticist; psychiatrist; epigeneticist; neurologist; biologist. Consecutive patients aged 18–50 years were recruited from 47 EU and USA psychiatric and neurological centres. Subjects needed to satisfy at least one of five criteria that specify varying combinations of psychosis, early-onset progressive cognitive decline and/or neurological or visceral symptoms characteristic of NP-C. *NPC1* and *NPC2* gene mutation analysis was performed in each subject.

Results: Of the 267 screened subjects, two were genetically diagnosed with NP-C (disease-causing mutations on both alleles) and 15 were considered as uncertain due to sequence changes in *NPC1* or *NPC2* genes detected on only a single allele. Few cases were genetically diagnosed with NP-C despite an enriched study population; this may reflect the rarity of NP-C. However the unexpected high occurrence of uncertain diagnosis suggests that further assessments such as full genome sequencing and biochemical tests are needed to optimise the identification of rare organic disorders in psychiatric and neurological populations.

Conclusions: The preliminary findings of a low proportion of genetically diagnosed NP-C patients and a larger proportion of subjects with uncertain diagnosis highlight a major challenge; the scarcity of cases to observe, which limits the body of evidence in rare diseases.

426. Relationship between Inflammatory Cytokines and Serum Uric Acid Levels with Adverse Cardiovascular Outcomes in Patients with Stable Coronary Heart Disease during Long-Term Follow-Up

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Background: So far it is unclear whether the association between serum uric acid (SUA), inflammatory cytokines and risk of atherosclerosis is causal or an epiphenomenon. The aim of the project is to investigate the independent prognostic relationship of inflammatory markers and SUA levels with adverse cardiovascular outcomes in a patient population with stable coronary heart disease (CHD).

Objectives: The aim of the project is to investigate the independent prognostic relationship of inflammatory markers and SUA levels with adverse cardiovascular outcomes in a patient population with stable coronary heart disease (CHD).

Methods: SUA, C-reactive protein (CRP) and interleukin (IL)-6 were measured at baseline in a cohort of 1,056 patients aged 30–70 years with CHD. Cox proportional hazards model was used to determine the prognostic value of these markers on a combined CVD endpoint during eight year follow-up after adjustment for covariates.

Results: For 1,056 patients with stable coronary heart disease aged 30–70 years (mean age 58.9 years, SD 8.0) follow-up information and serum measurements were complete and n = 151 patients (incidence 21.1 per 1,000 patients years) experienced a fatal or non-fatal CVD event during follow-up (p-value = 0.003 for quartiles of SUA, p = 0.002 for quartiles ofC CRP, p = 0.13 for quartiles of IL-6 in Kaplan-Meier analysis). After adjustment for age, gender and hospital site the hazard ratio (HR) for SUA increased from 1.53 to 1.74 and 2.80 in the second, third, and top quartile, when compared to the bottom one (p for trend <0.0001). The HR for CRP increased from 0.85 to 0.98 and 1.64 in the respective quartiles (p for

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trend 0.02). After further adjustment for covariates only SUA showed a clear statistically significant relationship with the outcome, whereas CRP did not.

Conclusions: The data suggest that serum uric acid levels predict future CVD risk in patients with stable CHD with a risk increase even at levels considered normal and therefore may contribute independently to the pathophysiology of CVD-events in patients with stable CHD.

427. Pharmacogeneticepidemiology

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Background: Pharmacogeneticepidemiology (PGxE) studies the range of responses to pharmacologic agents in relation to genetic variations in population groups.

Objectives: In order for pharmacoepidemiologists to get familiarized with PGxE in a broad manner, a description of what has been published up to date in PGxE will be given. A description of the different methods used will be presented and examples on how health authorities utilize the information published in PGxE will be provided.

Methods: PubMed was searched to identify all PGxE studies published up to December 31, 2011, using the keywords "pharmacogenetics" or "pharmacogenomics". Abstracts of studies were selected if the studies were written in the English language, if the research was conducted in humans, and if the authors had applied an epidemiological design. Descriptive statistics were performed.

Results: In total 810 abstracts were identified between 1995, when the first was published, and 2011. The most common design used was case control studies (81%). Genome wide association studies began in 2008 and represented 8% of the studies. Based on first author, 72% of studies were conducted by Academic researchers, and 5% by Industry researchers. Concerning outcome, 43% studied efficacy, 23% adverse effects and 20% pharmacokinetics or pharmacodynamics. Twenty-six per cent of the papers were related to psychiatric drugs, and 18% to oncological drugs. The most studied medications were antineoplastic drugs (18%), followed by antidepressants (9%). The majority of studies assessed polymorphisms related to genes in the CYP family (28%) and in the ABCB family (9%).

Conclusions: A total of 810 PGxE studies were identified in a period of 16 years. During the last years, new methods such as genome wide association studies have raised awareness of this relatively new field. Since PGxE covers a wide number of specialties and pharmacologic agents important in clinical practice, and helps predict the range of responses to pharmacologic agents, all types of institutions would benefit from the field. The majority of the studies were conducted in academia, thus a greater understanding and involvement from other pharmacoepidemiological institutes would be beneficial.

428. Increasing the Value of Retrospective and Prospective Real-World Registries with Pharmacogenomic Testing and an Integrated Personalized Medicine Approach: Opportunities & Challenges

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Background: A better understanding of patient genetic make-up through pharmacogenomic testing can help achieve improved and more predictable patient outcomes. Stakeholders including physicians, payers and patients can benefit from real-world data that identify, a priori, the sub-groups of patients for whom treatments are likely to be more effective and more tolerable.

Objectives: Underscore value of integration of pharmacogenomic testing as applied to registries using a case study approach; illustrate key scientific/operational challenges associated with this approach.

Methods: Retrospective/prospective case study designs within which pharmacogenomic testing has been integrated are presented. Key design parameters are described and scientific and operational challenges alongside strategies for resolution are delineated.

Results: As the genetic make-up of a patient does not change, pharmacogenomic testing can be done at any point in time and paired with historical and/or newly collected patient level data to achieve a robust dataset. Retrospective studies are highly efficient as they do not require costly longitudinal follow-up. Prospective studies, including registries, offer the opportunity to augment pharmacogenomic and other study data with patient and physician reported outcomes not otherwise available in the medical chart or other source of secondary data. Main challenges with either approach include optimizing patient informed consent process, streamlining logistics associated with pharmacogenomic testing and storage in the usual care environment, EU regulatory issues, complexity of data analytics in relation to the diversity of patient subgroups, and associated variability in outcomes which can emerge.

Conclusions: The integration of pharmacogenomic testing with real-world studies including disease registries offers an important opportunity to identify sub-groups of patients for whom treatment is more effective and tolerable. Alongside resource utilization and cost of care data, this patient-centered evidence can be used to inform clinical guidelines and physician/payer decision-making.

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429. Cancer Patients' Preferences for Pharmacogenetic Testing (PGx)

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Background: Pharmacogenetics is used increasingly to guide cancer therapy. We have shown previously that 98% of cancer patients (pts) are accepting of PGx. However, there is little knowledge of the factors influencing pts' acceptance of PGx.

Objectives: To determine and estimate cancer pts' preferences for attributes of PGx.

Methods: We interviewed 242 cancer pts regarding their preferences for PGx using quantitative choice-based conjoint analysis surveys. Potentially curative (adjuvant) pts received a survey focusing on the potential of PGx to predict for efficacy of chemo; metastatic pts received a survey focusing on its potential to predict for toxicity. Logistic regression analysis was performed to estimate utilities.

Results: Of 136 adjuvant pts: 43% male; median age: 56 years (20–82); 28% breast ca; 18% colorectal ca; 15% lung ca. Acceptance of PGx was most heavily influenced by cost of PGx (part worth utility [PWU] = 41) and the prevalence of the genetic variant associated with lack of benefit from chemo (PWU = 26); followed by wait time for results and the efficacy of the chemo being offered. Preferences for PGx fell at a cost of $1,500; women, pts in their 60s, college graduates, and pts diagnosed >1 year were most cost sensitive. Of 106 metastatic pts: 60% male; median age: 61 years (22–78); 26% lung ca; 23% colorectal ca; 5% breast ca. Acceptance of PGx was most influenced by cost of PGx (PWU = 49) and wait time for results (PWU = 31); and was relatively insensitive to the prevalence of the genetic variant associated with increased toxicity, or the toxicity profile of the chemo being offered. Preferences for PGx fell at a cost of $500; pts diagnosed >3 year, pts with income <$100,000 and aged >70 year were most cost sensitive. For all pts, preferences for PGx fell when wait time for results was >2 weeks, or the prevalence of the genetic variant of interest was <25%.

Conclusions: Cancer pts' acceptance of PGx is most heavily influenced by the cost of testing, with adjuvant pts accepting higher costs compared to metastatic pts. For all pts, preferences for PGx fell when wait time for results was >2 weeks, or the prevalence of the genetic variation associated with lack of efficacy/increased toxicity of chemo was <25%.

430. Pharmacogenetics of Warfarin in Children

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Background: Warfarin is a widely used anticoagulant for the prevention and treatment of life-threatening blood clots. However, its large inter-patient dose range combined with a very narrow therapeutic index results in numerous adverse drug reactions (ADRs). In adults it is well established that polymorphisms in three genes (CYP2C9, VKORC1, CYP4F2) significantly contribute to the inter-patient variability in the required warfarin dose. However, due to conflicting findings and the small number of studies conducted so far, the importance of genetics in warfarin dosing in children is unclear.

Objectives: To determine the effect of genetic variation in CYP2C9, VKORC1 and CYP4F2, as well as additional genes involved in drug biotransformation and coagulation pathways, on warfarin response in children.

Methods: We are performing an ongoing, retrospective observational study in paediatric patients who have received warfarin therapy. We will assess the associations of variants in VKORC1, CYP2C9 and CYP4F2 with (1) therapeutic warfarin dose, (2) time to stable international normalized ratio (INR), and (3) warfarin-induced ADRs. We will also investigate the associations of additional genetic variants in warfarin and coagulation pathways with therapeutic dose, and assess their importance in a multivariate context.

Results: Eighty paediatric patients have been recruited to date with a median age of 4.5 years (range, 0.2–17.8 years) at time of warfarin initiation. Based on initial clinical characterization, median stable daily warfarin dose was 3 mg (range, 0.75–10 mg) and median time to therapeutic INR was 5 days (range, 1–79 days). Additionally, 33.8% (n = 27) and 3.8% (n = 3) of patients experienced a bleeding or thrombotic episode, respectively.

Conclusions: The anticipated results of this study will provide insight into the genetic basis of warfarin outcomes in children. A paediatric-specific pharmacogenetic dosing algorithm may improve estimations of warfarin dosing in children and increase the accuracy of dose refinements. Furthermore, by using genetics to identify children who are at risk for over- or under-anticoagulation, we may improve the safety of paediatric warfarin

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therapy by reducing the incidence of severe warfarin-induced ADRs.

431. Manganese Superoxide Dismutase Polymorphism and Breast Cancer Recurrence: A Danish Population-Based Case-Control Study of Breast Cancer Patients Treated with Cyclophosphamide Epirubicin and 5-fluorouracil

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Background: Manganese superoxide dismutase (MnSOD), a mitochrondrial antioxidant enzyme, inhibits oxidative damage modulating the effectiveness of cancer therapy. A single nucleotide polymorphism (SNP) (Val16Ala) in the SOD2 gene, which encodes MnSOD, results in decreased MnSOD activity. Breast cancer patients treated with chemotherapy and who carry the Val16Ala allele may have an increased rate of breast cancer recurrence.

Objectives: We aimed to examine the association of SOD2 genotype and breast cancer recurrence among patients treated with cyclophosphamide-epirubicin-5-fluorouracil (CEF) chemotherapy, the current standard breast cancer adjuvant chemotherapy.

Methods: We conducted a case-control study of breast cancer recurrence nested in the population of female residents of Jutland, Denmark who were diagnosed with non-metastatic breast cancer between 1991 and 2001, received CEF adjuvant chemotherapy and were registered in the Danish Breast Cancer Cooperative Group. We identified 126 cases of recurrent or contralateral breast cancer and matched to them 241 controls on menopausal status, stage, calendar time and county. We genotyped the SOD2 (Val16Ala) allele. We used conditional logistic regression to compute the odds ratio (OR) and associated 95% confidence interval (95%CI).

Results: The frequency of the *SOD2* Ala allele was 70% in cases and 71% in controls; 40% vs. 44% were heterozygotes, while 30% and 25% were homozygotes, respectively. The odds ratios associating breast cancer recurrence with heterozygote and homozygote carriers of the Ala allele, vs. homozygote wildtypes, were OR = 1.1 (95%CI = 0.65, 2.0) and OR = 0.87 (95%CI = 0.47, 1.6, respectively).

Conclusions: Our study indicates that reduced MnSOD enzymatic activity has little, if any, impact on rates of breast cancer recurrence among patients treated with CEF.

432. Improved Drug Packaging Design Can Improve Patient Safety

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Background: Automatic generic substitution is standard in many countries. The main problem with generic substitution is patient compliance. Norwegian research shows that approximately 5% of Norwegians and 10% of immigrants used both the original and generic drugs at the same time. It has been suggested that improved packaging design could decrease patient errors.

Objectives: The objective of this study was to test if a new standardized drug packaging design could improve recognition and discrimination of drug packages.

Methods: We designed new drug packages with the active ingredient and strenght prominently displayed in the upper right hand corner. The new design was compared with the standard packages in a mental rotation test. This is a validated cognitive test used to measure recognition and discrimination performance. Our study was carried out on 30 older people (69–86 years, mean 75.9) and 29 students (18–38 years, mean 25.9). We measured the ability of participants to decide whether drug packages contained the same active ingredient or not, depending on packaging design.

Results: The important measures in a mental rotation task are accuracy (percent correct answers) and reaction time. With the new design, overall accuracy in the older group improved from 52 to 82% ($p < 0.001$) and in the young group from 79 to 94% ($p < 0.001$). In the older group, the accuracy improved from 44% to 86% ($p < 0.001$) when comparing packages with the same active ingredient. In both groups, overall reaction time decreased from 1,154 to 1,005 ms ($p < 0.001$).

Conclusions: Our study, the first to evaluate a new standardized design of drug packaging, shows that recognition and discrimination are significantly improved compared to manufacturers' original design. Especially, the ability to discriminate between packages with the same active ingredient improved form chance level to a high degree of accuracy. Our findings suggest that a standardized design may increase patient compliance and safety.

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433. Behavioural Assessment Offers Improved Evaluation of Risk Minimisation Tools (RMT)

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Background: RMTs must be evaluated as a requirement of both US REMS, and the EU-RMP. However, post launch evaluation of RMTs has mainly examined distribution (by coverage metrics), usage (by surveys) and knowledge (by questionnaires), which often does not correlate with showing the objective of the RMT is being met.

Objectives: A dynamic checklist tool, based on algorithm and decision choices, has previously been described [1]. This tool, together with a behavioural survey tool, which can be used to measure what actions prescribers actually take, was been developed and verified for use in RMT evaluation.

Methods: A dynamic real-time online behavioural survey has been produced, and administered at an interval after usage of paper based decision and educational RMT. The behavioural surveys were completed with a range of HCPs primarily in oncology and CNS therapy areas, although the method can be used in all disease and treatment categories.

Results: Both the dynamic real time checklist and the interval behavioural survey provided useful information on risk minimisation tool effectiveness, and allowed systematic improvements. The dynamic on line checklist permitted regular tool improvement, based on feedback, and not just at the time of formal regulatory reporting. On line delivery of tools appeared to be preferred delivery channel of tools and evaluation for EU HCPs.

Conclusions: We have shown the feasibility and efficiency of behavioural effectiveness assessment. It provides an improvement on current methodologies, and when combined with dynamic online checklist usage, offers cost savings and the chance the update tools more quickly. Online tools permit direct recruitment into registries, where available, which also allowing RMT and RMP evaluation to be linked to outcomes. For specialist RMPs, it may be appropriate to offer on line only tool delivery, providing easier evaluation, cost effectiveness, better version control whilst being preferred by HCPs over paper-based tools. [1] Banerjee AK, Ingate S et al. Real time post marketing evaluation of risk management plans (RMPs)- a novel pharmacoepidemiological tool? PEDS 2008:17:S81–82.

434. Safety Issues Seem To Occur More Often in Highly Innovative Drugs

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Background: Truly innovative new drugs often answer unmet medical need. They are usually first-in-class and class-related safety issues may not be fully identified at time of approval. This may put these drugs at risk of showing safety events early post marketing.

Objectives: To assess whether safety issues of highly innovative drugs are identified more frequently and rapidly than of other drugs.

Methods: A retrospective cohort study was performed of new drugs approved in Europe between 1999 and 2011 excluding vaccines and diagnostics. Drugs were classified according to their innovation [Motola, BJCP 2006] as A) important, B) moderate, C) modest or merely pharmacological/technological innovations. Comparison was made between highly innovative (A) and all other drugs. Safety issues were identified based on "dear doctor" letters (DHPCs) issued by the Dutch Medicines Evaluation Board or withdrawals. Outcome variables were frequency and timing of a first DHPC or safety-related withdrawal. Kaplan-Meier survival analysis and Cox-regression to correct for possible confounders were used to analyze the data.

Results: Innovativeness was assessed for 119 new drugs; 144 drugs, approved after July "04 are still being classified. Of those 119 drugs 32 (27%) were rated grade A. DHPCs were issued for 14/32(44%) with no withdrawals vs. 16/87(18%) with two withdrawals for other drugs ($p = 0.005$). In the 14 DHPCs for innovative drugs only three recommended to limit the indication and two added a contra indication. The probability of acquiring a DHPC for innovative drugs during 3 years follow up is 16% (95CI 3%; 28%) vs. 9% (95CI 3%; 15%) for other drugs and during 12 years 46% (95CI 28%, 65%) vs. 20% (95CI 11%, 29%), respectively (log-rank $p = 0.007$). Adjusted hazard ratio was 3.2 (95CI 1.5; 7.1) with no identified significant confounders.

Conclusions: Our preliminary data indicate that important safety issues are more often identified for highly innovative drugs that was observed continuously from 3 through 12 years after approval. This underlines the importance of close monitoring of safety of these drugs after registration. As no withdrawals were observed and only few indications changed, their therapeutic benefit appeared unchallenged.

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435. Medication Errors Related to Patches for Systemic Pain Relief in a Swedish Incident Reporting System

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Background: Medication errors are common, preventable and may cause harm to the patients. In Sweden medication errors are reported to local incident reporting systems.

Objectives: The purpose of this study was to describe medication errors concerning patches for systematic pain relief reported to one incident reporting system.

Methods: All reports of incidents related to drugs, submitted to the Östergötland county council (429,642 inhabitants) incident reporting system, Sweden, during the years 2004–2011 were included. A medication error was defined as a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient. Reports describing the use of patches for systemic relief of pain were selected. Based on the information in the reports, cases not describing medication errors were excluded. The included reports were scrutinized and relevant information was extracted.

Results: During the study period 13,617 incident reports, related to drugs, were submitted to the incidence reporting system. Of these, 277 (2%) mentioned patches and 157 (1%) were classified as medication errors involving patches for systemic pain relief. The substances in the reported medication error cases were fentanyl (135; 86%), buprenorphine (10; 6%) and unknown analgetic substance (12; 8%). The medication error was reported to cause harm in 31 (20%) cases, with inadequate pain relief being the most common consequence. In cases where harm was reported, the type of error was most often missed doses (n = 19) due to lack of routines ascertaining changes of patch or use of higher than prescribed strength/multiple patches (n = 4). In the patients where no harm was reported the type of error was most often missed dose (n = 38) or delayed change of patches (n = 33).

Conclusions: Most reported medication errors were related to use of fentanyl patches for systematic pain relief and did not cause harm. Inadequate pain relief due to missed doses was common in the patients where harm was reported. There is a need to ensure that routines for administration and documentation are followed to avoid these medication errors.

436. Effectiveness of Varenicline Medication Guide for Conveying Safety Information to Patients: A REMS Assessment Survey

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Background: Risk Evaluation and Mitigation Strategies (REMS) include a range of mechanisms to enhance patients'' safe use of medications. One mechanism is a patient Medication Guide (MG) that provides key information about a medication, including potential risks associated with the medication.

Objectives: To evaluate the effectiveness of the varenicline MG as part of the REMS, we undertook a survey among patients dispensed varenicline in a large health insurance plan in the United States.

Methods: Varenicline recipients identified within the Normative Health Information (NHI) database, a large United States administrative claims database, were invited to participate in a self-administered survey. Survey questions were both general (receipt and reading of the MG) and specific regarding potential varenicline risks of neuropsychiatric symptoms (3 questions), serious skin reactions (2 questions) and allergic reaction (2 questions).

Results: From 3,568 varenicline recipients invited to the survey, 640 (18%) responded (83% postal mail, 17% online), with 633 completing at least one of the three risk comprehension questions. The majority (85%) indicated receiving the MG with the medication, and (86%) indicated reading the MG. Of those completing at least one risk comprehension question, 91%, 41%, and 53% correctly answered at least one question on neuropsychiatric symptoms, skin reactions, and allergic reactions, respectively. Overall, a higher proportion of respondents who indicated reading the MG had correct responses to the risk comprehension questions than those who did not read it.

Conclusions: The varenicline MG was widely received and read among survey respondents. The information conveyed was generally well understood, although reasons for better understanding of the potential risks of neuropsychiatric symptoms than allergic or skin reactions remain unclear. This study provides an assessment of the effectiveness of the varenicline MG in communicating information about potential risks associated with the medication and measures that can be taken to mitigate them. This assessment method may be used to evaluate the effectiveness of MGs for other medications.

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437. Nurses' Attitudes and Adverse Drug Reaction Reporting

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Background: It is recognized worldwide that adverse drug reactions (ADR) are an important cause of morbidity and mortality. A voluntary reporting system is fundamental to drug safety surveillance. However, under-reporting among healthcare professionals is its major limitation. In this matter, nurses can bring fundamental information.

Objectives: Identify the knowledge and attitude-related factors associated with ADR under-reporting by nurses.

Methods: We conducted a case-control study, covering nurses working in the Northern Portugal. The 265 cases comprised nurses who had previously reported at least one ADR to the drug surveillance center from 2000 to 2010. The 1,060 controls comprised nurses who had never reported an ADR, who were stratified by the districts and randomly selected. Interviews were conducted using a self-administered questionnaire. Knowledge and attitudes regarding spontaneous ADR reporting were mostly based on Inman's "seven deadly sins". Agreement with the questions was measured using an unnumbered horizontal, continuous visual analogue scale. The answers were read in a range from zero to ten. We used a logistic regression to determine the ADR reporting adjusted odds ratio (ORadj) for a change in exposure corresponding to the interquartile range for each attitude.

Results: We received a total of 263 valid questionnaires and 39 null (response rate 20,5%). Reporting risk proved higher into nurses working in primary vs. hospital care (OR_{adj} 14.1; 95%IC 7.3–27.4). Concerning to the attitudes, hence, an interquartile decrease in any of the following attitude increased the risk of reporting: (1) two times for, *Indifference* ($1/IqOR_{adj}$ 1.8; 95%IC 1.1–3.0); (2) three times for, *Complexity of the system* ($1/IqOR_{adj}$ 3.4; 95%IC 1.8–6.3), and (3) two times for, *Misunderstanding of the system* ($1/IqOR_{adj}$ 2.3; 95%IC 1.3–3.9).

Conclusions: This study shows that there are certain attitudes of nurses associated with under-reporting. An educational intervention targeted to change these attitudes identified, may minimize under-reporting and contribute for the safety of patients. Our study also indicates that we must take into account the working place of nurses and their motivation to report an ADR.

438. Compliance Survey for Thalidomide Safety Use (part5); after Revision of TERMS

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Background: In Japan, thalidomide launched under a risk management program named TERMS (Thalidomide Education and Risk Management System) in Feb 2009. The compliance of TERMS has been surveyed and we have received no reports that the fetus was exposed to thalidomide as of December 15, 2011. However, TERMS was revised in March and September 2010 for a smoother system administration.

Objectives: Assess compliance of TERMS after revision.

Methods: The survey has been being conducted on phone or by document every six months about compliance of TERMS and the patients were asked to comment on TERMS. The results were reported from March 30, 2009 to December 15, 2011. We consider the revision of TERMS in September 2010 as final. The both results before and after the revision of TERMS were compared and statistically tested.

Results: Five thousand twelve people were requested to answer the questionnaires at starting TERNS (4,519 on phone, 493 by document), and 4,535 people were requested for follow up questionnaires (4,162 on phone, 373 by document). Among them, 2,830 people (25,26 on phone, 304 by document; 2,025 before the revision, 805 after), and 2,569 people (2,329 on phone, 240 by document; 1,079 before the revision, 1,470 after) were obtained, respectively. From the analyses of the answer, it was apparent that the compliance of TERMS was maintained even after the revision. In particular, after the revision, the patients tend to be introduced about the procedure with TERMS by co-medical staff ($p < 0.001$). Moreover, it is desirable that the results showed the patients' correct knowledge of the management about the partners' pregnancy ($p < 0.001$) after the revision.

Conclusions: The patients with TERMS have some distress. We obtained the compliance of TERMS after the proposed revision by us.

439. Evaluation of Bayesian Methodology for Use in Manufacturing Related Automated Signal Detection with Batch(lot) Specific Adverse Event Reports

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Background: Various methods of signal detection exist that assess disproportionality of adverse events (AEs), with minimal agreement on the most appropriate methods that take into account factors such as low event counts,

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multiplicity of testing, and variable reporting rates in spontaneously reported AEs. Furthermore, limited data and tools are available to assess batch(lot) specific AE reports for marketed products.

Objectives: To compare the use of proportional reporting ratio (PRR) to empirical Bayes (EB) methods (single and a mixture of two gamma distributions) in automated signal detection (ASD) for batch (lot) specific AEs. The primary focus is on identification of manufacturing related signals.

Methods: Analysis using spontaneous AE data compares findings assessing the association of AE by batch(lot) combinations using four methods: (1) PRR; (2) EB lower limit of the 90% CI (EB05) for the posterior distribution of the event rate (λ), modeled as the gamma distribution resulting from gamma prior for λ and Poisson distribution for the likelihood function; (3) EB05 for truncated Gamma-Poisson mixture based on data with all AE by batch (lot) combinations with zero events excluded, and; (4) EB05 for posterior distribution of λ modeled using a mixture of 2-gamma distribution as the prior. Targeted MedRA high level terms (HLT) and clinical review are used to determine the most appropriate method for ASD for batch (lot) specific AE reports.

Results: Preliminary results show striking differences in the number and types of potential signals identified. This pilot is ongoing, final results are forthcoming, and will be presented at the conference. Thus far the PRR has detected significantly more signals of disproportionality than either of the Bayesian methods.

Conclusions: Preliminary results show that each of the methods produced a variable number of signals. Evaluation of each of these methods, including clinical judgment, is necessary to determine which is most appropriate.

440. New Medical Products Governance in France: What Is the Impact on Post Approval Studies Requested by the French Health Authorities

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Background: In Europe, France is one of the largest potential markets for new medical products, with strict regulations for drugs and medical devices that have an uncertain risk/benefit profile. However, recent drug scandals have shown inadequacies in the countries regulatory climate.

Objectives: To provide an overview of what changes will occur in Drugs/MD governance pledge reform in France after the recent diabetes drug scandal.

Methods: The information displayed by the French Health Agencies regarding the revamp of the Medical Regulatory System have been studied to provide a comprehensive analysis concerning the expected impact on post-approval studies.

Results: There are two agencies involved in the process of Drug/MD approval: The National Safety Agency (ANSM), responsible for market authorization and safety follow-up and the National Health Agency (HAS), in charge of the evaluation of intrinsic value of a Drug/MD. To enhance collaboration between the two entities, and avoid overlapping requests for post-approval studies, a partnership has been formed between the two agencies. Separately, HAS has published guidance documents on post-approval studies and ANSM will be able to charge pharmaceutical companies with penalties in the event of distortion or delay in the communication of study results. In conjunction, a strict surveillance of potential conflict of interest and disclosures for external experts and steering committees will be put in place. Additionally, the new law includes an entire chapter making it obligatory that all direct and indirect benefits that pharmaceutical companies provide to healthcare professional, patient associations, scientific societies and specialized media be made public.

Conclusions: The strategy of the new governance regulations regarding medical products security in France won't change directly the environment of post approval studies requested by the competent authority. Instead, the role of Health Agencies will be reinforced by applying the precautionary principle.

441. Are General Sales List (GSL) Medication Labels and Patient Information Leaflets Adequate?

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Background: Studies in some countries have reported incomplete and/or inconsistent patient information on package inserts of medicinal products, potentially causing patient confusion and medication errors.

Objectives: To evaluate the adequacy of labeling information on selected General Sales List (GSL) medicines (also known as over-the-counter medicines) in Singapore.

Methods: We conducted a cross-sectional comparative evaluation of patient information provided on product labels (outer cartons and inner labels) and patient information leaflets (PILs) of GSL topical antifungal products that were available for retail sale in Singapore. We evaluated the labeling information for completeness using a 17-point completeness scoring system based on fulfillment of 17 labeling requirements listed by the Singapore Health Sciences Authority; for accuracy by comparing with drug information references; for clarity by assessing the use of scientific or lay language and any ambiguity of instructions; for within-product consistency of information between the product labels and PIL of each product; and across-product variability of labeling information. Qualitative analyses and descriptive statistics were performed.

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Results: Of 51 products evaluated, the median completeness score was 12 (range: 5–16). Although no product fulfilled all 17 labeling requirements, most provided information necessary for safe use of the products, including contraindications (76.5% of the products), side effects/precautions (86.3%) and when to consult a doctor (78.4%). Information for use during pregnancy and lactation was provided in only 39.2% and 15.7% of the products, respectively. All products provided largely accurate information. However, only 29.4% provided all the patient information in lay language. In addition, clarity of information in some products was affected by spelling/grammatical errors (17.6%) and within-product inconsistencies (15.7%).

Conclusions: Labeling information varied across the evaluated GSL antifungal products. This raises a need to improve the adequacy of labeling information across GSL medicines for their safe and effective use by patients.

442. Assessing Current Public awareness of Anti-Counterfeiting Measures in Health Products

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Background: Currently, legitimate manufacturers employ different anti-counterfeiting measures in health products to combat counterfeiting and to safeguard public health. Little is known if the public is aware of such measures for product authentication.

Objectives: To assess the current public awareness of anti-counterfeiting measures in health products, as well as awareness in relation to perception and behavior.

Methods: We conducted a cross-sectional survey at various public locations in Singapore. A self-designed questionnaire was used to assess the awareness, perception, and behavior of the public on anti-counterfeiting measures. Pre-testing of the questionnaire was conducted before the actual survey. The targeted survey participants included citizens or permanent residents of Singapore, who were 21 years and above, and were willing to participate in the survey. Statistical analyses were performed using SPSS software (version 19). Chi-square tests were performed to evaluate awareness in relation to perception and behavior towards anti-counterfeiting measures. A p-value of <0.05 was considered statistically significant.

Results: Four hundred participants were surveyed between December 2011 and January 2012. Of the 308 who had ever purchased health products, 40.6% ($n = 125$) perceived themselves to be aware of anti-counterfeiting measures in health products, but only 10.1% ($n = 31$) demonstrated awareness as assessed from our study. Their awareness of anti-counterfeiting measures in health products was significantly associated with their perceived level of confidence (on a five-point Likert scale) in differentiating counterfeits from genuine health products ($p < 0.001$) and with their practice of checking if the health products they purchased were genuine or counterfeit ($p < 0.001$).

Conclusions: In Singapore, public awareness of anti-counterfeiting measures in health products appears to be lacking. Our findings suggest a need to raise public awareness in order to promote the practice of checking health products during purchase and to increase consumer confidence in safeguarding themselves against counterfeits.

443. Healthcare Professionals' Attitudes towards Adverse Drug Reaction Reporting in Nepal: A Factor Analytic Study

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Background: Healthcare professionals' attitudes towards adverse drug reaction (ADR) play vital role to report any encountered cases of ADR in their routine clinical practice. Inman has proposed "seven deadly sin" within healthcare professionals which potentially discourage them to report ADR cases. Besides, there are other proposed reasons for under-reporting by different studies.

Objectives: To identify the factors discoursing ADR reporting among healthcare professionals.

Methods: We conducted a cross-sectional study among healthcare professionals; doctors, nurses and pharmacists; working at four Regional Pharmacovigilance Centre (RPC) of Nepal. Validated self-administered structured questionnaires were randomly distributed to 450 healthcare professionals. The questionnaire was designed to five level likert scale (one strongly disagree and five strongly agree). Exploratory principle components analysis of attitudes towards factors discouraging ADR reporting was carried out applying varimax rotation.

Results: Overall 333 questionnaires were received yielding a 74.0% response rate. Respondents included 162 doctors, 135 nurses, 32 pharmacists, with four respondents who did not mention their qualification. Exploratory principle components analysis of attitudes towards factors discouraging ADR reporting produced three components above the loading over 0.5. The three components included insecurity, conservative attitudes, and exhaustion.

Conclusions: This study identified factors discouraging Nepalese healthcare professionals' to report ADR. Appropriate interventional as well as non-interventional methods to generate positive attitudes would improve the reporting rate among healthcare professionals.

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444. In-Site Measuring of the Role of Educational Package To Increase GPs' Awareness of ADR Reporting System

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Background: The reporting of adverse drug reactions (ADRs) is fundamental to the safety surveillance of medicines. The leading role in the process of discovery and reporting an ADR belongs to physicians. Our study hypothesis was based on literature research that doctors' attitudes and knowledge of ADR reporting schemes are determinants of reporting rates.

Objectives: The main objective of the study is to assess the knowledge of general practitioners (GPs) of the pharmacovigilance system and determine the influence of education for improving their willingness to participate in the "yellow card" scheme.

Methods: A representative sample of 63 GPs from the registered practices on the territory participated in the study. An initial in-site interview was conducted assessing their attitude and knowledge of the pharmacovigilance system. A package of preliminary prepared educational materials (leaflet, standing reminder card, brochure translated in Bulgarian – WHO/EDM/QSM/2002.2 and CD with legislative documents and presentations) concerning the reporting of ADRs was distributed to each physician. After one month, an outgoing interview was carried out to evaluate the impact of the educational materials. A statistical analysis including descriptive statistics and non-parametric tests was used.

Results: The results of the intial interviews show that 34.9% of the GPs are acknowledged with the ADR reporting system while this percentage in the outgoing interview is 51.2% (32% alteration). The whole share of the respondents who consider having any knowledge of the "yellow card" system rises from 55.5% to 80.6% ($p < 0.05$). The number of GPs who consider the reporting of ADRs as their basic responsibility has not significantly changed – from 46% to 61.3% ($p > 0.05$). 87.1% of the participants consider the provided educational package useful for their everyday practice.

Conclusions: The GPs' level of awareness of the Bulgarian ADR reporting system is not sufficient. A significant share of the responders does not consider ADRs reporting their responsibility. Conducting education activities and distributing promotional materials is a possible intervention to improve the reporting rates.

445. Sources of Information Supporting Drug Withdrawal from the Market Due to Safety Reasons

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Background: Market withdrawal of medicines due to safety reasons is described to be preceded by a safety signal generation. Different methodologies for safety signal generation have been advanced, although a gold standard hasn't been reached. Furthermore, the confirmation of the previously generated signal is needed using safety data to assess benefit/risk ratios to support medicines withdrawal decisions.

Objectives: To identify the sources of information used by drug regulatory authorities and by pharmaceutical companies to support the decision-making process leading to the withdrawal of medicines from the market due to safety reasons.

Methods: A questionnaire was developed and sent to the medicines agencies of countries belonging to the Program for International Drug Monitoring of the World Health Organization (PIDM/WHO) in order to identify: (1) medicines market withdrawn from 1990 to 2010 and, (2) sources of information on which safety signals and withdrawn decisions relied. Sources of information were classified according to: (1) spontaneous reports, case reports and case series; (2) clinical trials; (3) observational studies; (4) review of all safety data available; (5) animal and other laboratory studies and (6) meta-analysis of clinical trails.

Results: The WHO and 97 of the 104 PIDM/WHO member agencies were contacted, of which 72 replied. For the studied period a total of 142 medicines were identified as withdraw from the market. Spontaneous reports, case reports and case series were the source of information for signal generation for 86 (61%) cases, followed by clinical trials, 22 (15%), animal and other laboratory studies 12 (8%), observational studies, 10 (7%), review of all safety data available, 10 (7%) and meta-analysis of clinical trials 2 (2%).

Conclusions: Spontaneous reports, clinical case reports and case series are the main source of information in supporting the decision-making process of medicines withdrawn from the market due to safety reasons.

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446. Non-Response in a Pharmacy and Patient Based Intensive Monitoring System

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Background: Worldwide pharmacists play an increasingly important role in pharmacovigilance. Web-based intensive monitoring, WIM, is a new form of active pharmacovigilance where pharmacists play a key role. Patients using drugs which are monitored are identified in the pharmacy and invited to participate in the active monitoring. Not all patients who are invited will eventually participate.

Objectives: The aim of this study is to investigate non-response bias in WIM. In addition, reasons for non-response will be investigated in order to identify barriers for participation.

Methods: The study population consisted of patients who received a first dispensation of an anti-diabetic drug monitored with WIB between 1 July 2010 and 28 February 2011. Possible non-response bias was investigated by comparing age, gender and the number of drugs used as co-medication. Reasons for non-response were investigated using a postal questionnaire.

Results: Responders were on average 4.5 years younger and used 0.8 co-medication less. There were no differences regarding gender. The main reason for non- response was that information in the pharmacy lacked. Among the patients who received information, and had access to internet but chose not to participate, little personal gain was a reason for non-response.

Conclusions: The differences between responders and non-responders should be taken into account when analyzing and generalizing data collected through WIM as it might contribute to non-response bias. The relatively high response to the postal questionnaire, together with the answers about reasons for non-response show that patients are willing to participate in a web-based intensive monitoring system. The information given in the pharmacy is crucial for their actual participation as such.

447. Patients' Motives for Participating in Active Post Marketing Surveillance

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Background: In a web-based intensive monitoring system, patients the direct source of information . To date little is known about patients' motivation to participate in active post marketing surveillance (PMS). Increased insight can help us to better understand and interpret patient reported information. It can also be used for developing and improving patient based pharmacovigilance tools.

Objectives: The aim of this study is to gain insight into patient motives for participating in an active PMS and investigate their experiences with such a system.

Methods: A mixed model approach combining qualitative and quantitave research methods was used. Semi-structured, in-depth, face-to-face interviews were the basis for questionnaire development. The questionnaire contained questions regarding patient demographics and questions relating to their participation in an active PMS system. Descriptive statistics were used to get an overview of the patient's characteristics, motives for participation and experiences with the system. Relations between patient characteristics and motives were analyzed using either a *t*-test or a Chi-squared test.

Results: One thousand three hundred thirty-two (54,6%) patients responded to the questionnaire. The main motive for participation was altruism, for example "*Other patients can be treated better"* (89%) and "*I want to help health care workers"* (84%). Often experiencing ADRs or bad experiences with drugs are not important motives. The patient's gender plays a role in the different motives for participation. The overall opinion about the system is positive.

Conclusions: The knowledge that patients participate in this kind of research from an altruistic point of view will supports the need of patient involvement in pharmacovigilance.

448. Public Awareness of Adverse Drug Reactions and Pharmacovigilance System in Korea

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Background: As more medications we used, the more frequent adverse drug reactions (ADRs) we encounter. To use drugs safely, we have to establish ADR reporting system and let the public be aware of it.

Objectives: The purpose of this study was to evaluate the attitude and knowledge of the public on ADRs and pharmacovigilance system.

Methods: A survey was performed using a structured questionnaire on 338 townspeople who participated in a health fair in Seoul and 202 subjects visiting the outpatient clinic in Seoul National University Hospital between 1st September and 30th September 2010. The results were statistically analyzed by using the SAS Program. Chi-square test was conducted.

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Results: Among 540 respondents, 79.6% have ever used drugs in recent three years. Among subjects who ever took medicine in recent years, 14.5% of publics and 34.7% of outpatients experienced ADRs. A majority of the respondents (93.1%) recognized ADRs as preventable partly or completely. Responsibilities of compensation for ADRs were mainly attributed to physicians (62.2%) and pharmaceutical companies (32.4%). Although 91.1% of the respondents agreed that a national ADR reporting system should be established, only 23.3% were aware of the currently existing spontaneous ADR reporting system in Korea. More than half (53.5%) of the study subjects responded simplification of reporting process is needed to activate spontaneous reporting system in Korea in the future.

Conclusions: The majority of respondents ever took medicine and a fourth of them experienced ADRs. The great majority of respondents agreed on the necessity of ADR reporting but did not recognize the existing pharmacovigilance system. Therefore the education and campaign for the public should be reinforced in order to improve public awareness.

449. A Nine-Year Review of Adverse Events Related to Chinese Herbal Medicine *Rhizoma Atractylodis* Contaminated with Tropane Alkaloids (2002–2011) in Hong Kong

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Background: *Rhizoma Atractylodis* (RA) is a popular Chinese herbal medicine (CHM) commonly used clinically to remove dampness. RA is the dried rhizome of *Atractylodes lancea* (Thunb.) DC. or *Atractylodes chinensis* (DC.) koidz. (Fam. Compositae). It should be non-toxic, and yet, from time to time anticholinergic poisoning related to use of RA have been reported.

Methods: Based on an adverse incident reporting system on CHM, poisoning cases related to consumption of RA were reviewed to identify any risk factors and hence prevention and control measures. Case records and investigation reports from January 2002 to May 2011 were retrieved, descriptive statistics were used and literature review was conducted.

Results: A total of 11 cases of anticholinergic poisoning relating to consumption of RA were identified. Eight (72.7%) were female and three (27.3%) were male. The age ranged from 9 to 52 years with a median of 45 years. Two-third of the cases had <1 hour's onset time. The majority had consumed RA during spring-summer (i.e., between April and August). The presence of tropane alkaloids was detected in the urine of six patients. From investigation reports, tropane alkaloids were detected in four of supplier's RA samples which come from imports.

Conclusions: Epidemiological findings are compatible with the pattern of use of RA. Contamination of RA by tropane alkaloids have likely occurred at upstream of the supply chain. Moreover, the competence of Chinese medicines traders and practitioners to identify and control the quality of the CHM at retail level are important to protect public health. Professional training, trader and public education would need to be enhanced to raise the awareness of herb contamination and ensure proper identification of the CHM. Targeted effort in spring-summer time (i.e., from April to August) is highly desirable.

450. Patient Reported Outcomes (PRO) Are Key to Post Launch Safety and Risk Management

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Background: PROs may identify safety signals earlier, in higher volume, in patient-relevant language with QoL measures. PROs may provide a richer patient-focussed picture of the safety profile of drugs with more accurate real-world ADR incidence/prevalence and online AE reporting can improve patient satisfaction with treatment. However validated methodologies, scope and data sets are needed.

Objectives: The industry/ academic/ regulatory supported PROSPER (Patient-Reported Outcomes Safety Event Reporting) Consortium was convened to:

1. Champion PRO use as a novel source of useful real-world efficacy and safety data (Defining PROs value in providing real-world efficacy and safety information and identify applications and where PROs can be useful)
2. Defining a standard for validating PROs and information sources. (Methodologies for PRO information collection, analysis and dissemination; Defining PRO-AEs and differences from consumer reports; and a core data set for PROs and PRO-AEs?)
3. Define an effective process for PRO use (Safety reporting standards (PRO-AEs) for PRO websites; valid v invalid data sources (e.g., non-industry sponsored Facebook websites); Developing a framework/guidance for using PROs and PRO-AE information?)

Methods: Literature review and consortium meetings to filter prioritise and draft consensus guidance outlines which were critiqued and tested against published evidence where available. Hierarchy/validity of evidence was based on published criteria.

Results: Draft validated cross industry guidance on patient provided data and the PRO methodology used to generate and validate it, with a particular focus on harms and benefits of medicines, was developed. A core definition, and data set for signal evaluation was produced, together with aceptable methodologies and a process for verification of different methods.

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Conclusions: PROs can be used for: safety evaluation (e.g., enhancing pharmacovigilance); Risk Management/ post authorisation safety and efficacy studies (PASS/ PAES); evaluating the effectiveness of risk minimisation; improving patient treatment adherence; enhancing public safety/risk communication. The draft guidance presented needs further consultation prior to adoption.

451. Double Standard for Risk Minimization Program for Thalidomide in Japan

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Background: In October 2008, thalidomide was approved by the Ministry of Health, Labour and Welfare (MHLW) on condition that the manufacturer implements the Thalidomide Education and Risk Management System (TERMS) capable of the real time monitoring of prescription/dispensing of thalidomide and pregnancy test results. Under the TERMS, the use of thalidomide is restricted to the patients with multiple myeloma (MM). For disorders other than MM, thalidomide is still imported by the individual doctors and those patients are registered to the Safety Management system for Unapproved Drugs (SMUD) introduced by the MHLW in 2009. The SMUD is a web-based registration system without the capability of the real time intervention. Some patients with MM are also registered to the SMUD.

Objectives: To estimate the number of females of child bearing potential (FCBPs) registered to the TERMS and SMUD.

Methods: The number of patients registered to the SMUD and TERMS was obtained from the website (http://www.smud.jp/ and http://www.fujimoto-pharm.-co.jp/jp/iyakuhin/thalido/). We estimated and compared the fraction of FCBPs in patients with MM, oncological diseases other than MM (ODs) and other diseases (non-ODs).

Results: A total of 530 patients (288 males and 242 females) were registered to the SMUD from March 2010 to December 2011 where the number of patients was 140 (mean age:70.7 years old; females: 55.0%), 277 (63.9 years old; 45.9%) and 113 (60.4 years old; 33.6%) and the number of FCBPs was 1 (0.71%; exact 95% CI:0.02–3.92%), 14 (5.1%; 2.8–8.3%) and 13 (11.5%; 6.3–18.9%) for MM, ODs and non-ODs, respectively ($p < 0.0001$ by the chi-square test for the difference of the proportion of FCBPs). The number of patients (with MM) registered to the TERMS between October 2008 and early February 2012 was 5732. The number of FCBPs under the TERMS was estimated to be 41 (2–225).

Conclusions: Although the SMUD is smaller, the estimated number of FCBPs in the SMUD (28) was more than half of that in the TERMS (41). This indicates that patients with higher risk of pregnancy are covered by the weaker system (SMUD). The unification of two systems or, as the second best option, enhancement of the SMUD is desirable.

452. Examining the Readability of Two Package Inserts for Self-Medication in South Korea

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Background: Legal process is ongoing to allow remedies for minor illnesses to be sold without professionals' supervision in Korea. One of keys in ensuring that a patient uses drugs safely and effectively in the absence of professional support is drug labelling, which has been seldom stressed in Korea.

Objectives: To explore the readability and comprehensibility of the information contained on two package inserts.

Methods: A cross-sectional survey. Two package inserts (acetaminophen and cold remedy containing acetaminophen) were tested among 51 potential consumers. Participants were recruited from the first year undergraduate students in the Business Administration Department. Participants underlined words they could not understand fully or partially and answered 10 scenario questions. Primacy outcomes were the numbers of underlined words and the percentage of correct answers. Any differences between participant characteristic groups were tested by student *t* test, qui-square test or Fischer's exact test.

Results: More than 80% of participants properly replied in straightforward questions relating to indication, dosage, duplication, use in pregnancy and contraindication, but 73% about formulation. Less than half answered correctly in use of kids (41%) and in side effects (35%), when they were asked with multiple choice formats. Only 37% of participants could precisely indicate the duplication of active ingredient in two study drugs. Participants identified 118 words which they hardly understood. The names of drugs or diseases were frequently ranked high. Some of participants felt challenged by sentences as well as individual words. Little discrepancy was observed in the comprehensibility between participants' characteristics although female participants reported less number of words they could not understand ($p = 0.011$).

Conclusions: Korean consumers may face challenges to understand drug information due to technical terms understandable only to professionals and out-of-date expressions provided by the current package inserts. To secure safe and effective use of over-the-counter agents, greater efforts should be made to develop a more consumer friendly label.

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453. Minimizing Patient Medication Errors: The Role of Anxiety in Self-Injection Failures

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Background: Minimizing drug self-administration errors is an important target for pharmaceutical risk minimization. Some anti-tumor necrosis (anti-TNF) agents can be self-administered subcutaneously. Despite significant benefits associated with self-administration, self-injection can be challenging for some patients. Psychological factors, particularly injection anxiety, may play a role in this regard. Importantly, such factors are amenable to risk minimization interventions.

Objectives: To determine whether injection anxiety predicts self-injection failures.

Methods: Anti-TNF treatment patients were recruited and assessed for socio-demographics, hand dysfunction, and feelings about self-injection using the validated Self-Injection Assessment Questionnaire (SIAQ). Participants were assigned to one of three training conditions (written instructions only; in-person training; in-person training with time delay) and asked to perform a self-injection using a placebo-filled pen or syringe.

Results: One hundred twenty-one participants were recruited. Sixty-seven per cent were female and average age was 49.6 years (±13.4). Fourty-nine per cent had rheumatoid arthritis (RA), 20% had Crohn's Disease (CD), and 31% had plaque psoriasis (Ps). Fourteen per cent reported high injection anxiety (SIAQ value of between 0 and 3) at baseline. The correlation coefficient between self-injection experience and injection anxiety was 0.217 ($p < 0.017$) (higher SIAQ score = lower anxiety). Injection failures were experienced by 12 participants. A logistic regression analysis controlling for age, sex, years diagnosed and experience self-injecting (yes/no) showed that those with higher injection anxiety at baseline were 1.24 times more likely subsequently to fail when self-injecting ($p < 0.047$).

Conclusions: Results indicate that the higher a patient's anxiety level is prior to self-administering a medication the greater the likelihood that he/she will have an unsuccessful injection. Such findings are consistent with prior research. Screening patients for injection anxiety prior to self-injection training can help to identify those most in need of additional support in regard to self-injecting. Patient instructions might also be enhanced by including messaging addressing self-injection anxiety.

454. Indicators of Drug-Seeking Aberrant Behaviours during Post-Marketing Use of Fentanyl Buccal Tablets: Risk Scores in Support of Risk Management

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Background: Problematic prescription drug use includes misuse ("non-medical use"), addiction and unsanctioned diversion, and is reflected by drug-seeking aberrant behaviours. As part of a Modified Prescription-Event Monitoring study of Effentora® (fentanyl citrate buccal tablet; Cephalon), use of risk scores is being explored to identify patients at elevated risk of addictive behaviour and/or with aberrant behaviours.

Objectives: To characterise the nature and types of indicators of aberrant behaviour and risk factors for dependence reported during Effentora® [/sup]treatment.

Methods: An observational cohort post-marketing surveillance study. Exposure data from dispensed prescriptions issued by general practitioners (GPs) March 2009-April 2011. Outcome data (including events, selected clinical characteristics) from questionnaires sent to GPs 6+ months after 1st prescription for each patient. Questionnaires requested potential risk factors for substance misuse (dependence/addiction indicator) and aberrant behaviours (abuse indicator). Descriptive statistics and simple (non-weighted) risk scores were constructed on aggregate counts for indicators.

Results: Final cohort = 551 patients. Factors associated with dependence (% cohort): smoking = 21.6%, alcohol misuse = 3.3%, psychiatric disorders = 7.6% and previous history of substance misuse = 1.6%. Most patients had no factors associated with dependence (73.7%, risk score = 0); 26.3% had risk score ≥1. Aberrant behaviours reported (% cohort): overwhelming focus on opioid issues = 2.4%; escalating drug use = 5.3%; unclear aetiology of pain = 4.0%; loss of medication = 1.1%; multiple requests from different prescribers = 1.6% and unsanctioned diversion = 0.2%. Most patients had no aberrant behaviours reported (91.8%, risk score = 0); 8.2% had risk score ≥1.

Conclusions: The frequency of aberrant behaviours and indicators of dependence was low, though there were potential risk factors for misuse reported in some patients. Risk scores could provide useful tools to inform on post-marketing risk management of products. Identifying/studying such indicators is a useful research approach, however further development work is needed.

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455. Completing Epidemiology Questionnaires Incorporated into Cancer Clinical Trials: A Patient Preference Analysis

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Background: Collecting epidemiological data can help discover associations between epidemiological factors and disease propensity or outcomes, and is critical in the new area of personalized medicine. However, to date, little data has been collected to evaluate the willingness of clinical trial patients to complete these questionnaires.

Objectives: To assess patient willingness to complete epidemiological questionnaires if incorporated into clinical trials.

Methods: Cancer patients were interviewed to identify their levels of interest using hypothetical scenarios. Patient preferences and demographic information were analyzed using chi^2 tests.

Results: Six hundred ninety-two patients [51% female, median age of 59 year (18–91)] of all solid/liquid tumor diagnoses from a tertiary cancer centre, an academic hospital, and a community hospital were asked directly whether they were willing to complete an epidemiological questionnaire in addition to normal clinical trial procedures. Eighty-eight per cent answered affirmatively, 4% would not answer such a questionnaire under any circumstances, 5% were unsure, and 3% opted out. Fourty-four per cent were willing under any circumstances (i.e., adamant). Patients were more adamant if they had better performance status (ECOG 0–1 vs. 2–4; 49% vs. 30% $p = 0.002$). Preference for the length and timing of such questionnaires was also asked about. If delivered in a single visit, an average of 5.2 pages (SD 5.3) or 30 questions (SD 28), and of 15 minute (SD 9.0) duration was considered acceptable. Over several visits (as can happen in a clinical trial), patients accepted 3.3 pages (SD 3.1) or 21 questions (SD 20), requiring 10 minute (SD 7.7) per visit, over 2.2 visits (SD 0.7). Seventy-one per cent wanted the questionnaire to be voluntary. Patients generally preferred paper-based questionnaires (49%); 32% preferred electronic-based, and 18% had no preference.

Conclusions: Cancer patients overwhelmingly agreed to complete a variety of formats for voluntary, short epidemiological questionnaires when included in a clinical trial. Performance status was associated with willingness. In-depth correlations to the types of questions patients would accept (habits, sexual history, etc.) will be presented at the conference.

456. REMS – Lesson Learned from Effectiveness Assessments

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Background: In 2007, FDA Amendments Act granted FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) for drugs associated with serious safety risks. FDA issued a draft guidance to industry on the format and content of REMs. This guidance does not address methods to assess effectiveness of REMS programs. As sponsors of products with REMS, we have had experience assessing REMS with communication plans for patients and health care providers (HCPs) as well as REMS with Elements to Assure Safe Use (ETASU).

Objectives: To utilize various methods, including surveys and interviews, to assess effectiveness of communicating risks related to a product with a REMS program.

Methods: Surveys were initially developed and conducted to assess patient and HCP understanding of the risks described in the REMS program, as well as receipt of product-specific communications. For topics with patient and HCP understanding less than desired, follow-up interviews were conducted to better understand the root causes of those results.

Results: We identified multiple causes for the lower than desired understanding of risks for the REMS products beyond the quality and availability of written materials (e.g., Med Guides, product labels, HCP letters) to respondents: (1) complexity of survey questions led to unexpected answers that did not reflect respondent awareness or understanding; (2) relevance was a common theme where patients were not interested in risks that did not specifically pertain to them, (3) some patients had emotional reasons for not responding to risk information; (4) many physicians distrusted information provided by pharmaceutical companies and preferentially accessed alternate sources for product information.

Conclusions: REMS program assessments should consider a multi-modality approach to assess the effectiveness of a REMS with a communication plan, including consideration in the design, implementation, and measurement. These lessons should also be utilized to help develop future guidances and standards.

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457. Lessons Learned with Risk Minimization Activities in the US and EU

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Background: In recent years, safety legislation in the US and EU requires sponsors to implement risk minimization plans (RMiPs) to manage risks and ensure the benefits outweigh the risks for a medicinal product. We have observed variability in the types of risk minimization activities (RMAs) commonly used and their effectiveness across regions.

Objectives: To provide examples of RMAs required in the US and EU and discuss whether specific approaches are more or less effective across regions. In addition, considerations for the development of RMiP for the launch of a global product will be described.

Methods: Comparisons between the RMAs required in the US and EU will be presented along with a qualitative discussion of the strengths and limitations of these activities and their effectiveness in achieving risk minimization objectives.

Results: There are many different approaches to minimize the same risk of a medicinal product across regions. These may include such activities as communication plans, training/educational programs, registries, laboratory tests, drug utilization studies, and/or controlled distribution. The selection of the RMAs may vary across regions due to the differences in country-specific regulatory requirements and medical practice. In addition, there are varying expectations about how best to measure effectiveness of these activities, which continue to evolve.

Conclusions: In addition to labeling and pharmacovigilance activities, a sponsor should determine if there are significant risks that can impact the benefit-risk balance and plan RMA accordingly. While planning for RMAs the sponsor should consider the country-specific regulations and the practice of medicine in the region. Methods for evaluation of effectiveness need to be considered as part of the approach a priori.

458. Specialist Cohort Event Monitoring Studies at the Drug Safety Research Unit – A New Paradigm

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Background: Specialist Cohort Event Monitoring studies have been developed at the Drug Safety Research Unit (DSRU) in response to a need to provide drug safety surveillance in secondary care settings to complement that already well-established in primary care through it's techniques of Prescription Event Monitoring (PEM) and more recently in modified PEM studies. Already many of its studies are undertaken at the request of the UK medical regulator, the MHRA, as part of a Risk Management Plan (RMP) for a newly-licensed drug.

Objectives: In the UK, often the choice of drugs prescribed in primary care is guided by clinical experience and recommendations from experts and therapeutic committees in secondary care. In order to recognise this and to fulfil this safety surveillance need, the DSRU have now adapted the principle of PEM to prospectively monitor the use and safety of a new drug prescribed to a patient population under the care of specialists. This new methodology has developed in parallel with the new European Medicines Agency (EMA) regulatory requirement for pharmaceutical companies to undertake a Risk Management Plan as part of the post-marketing safety monitoring on some of their newly-licensed drugs.

Methods: Patients are identified through a network of specialists, and data on individual patient's general health, medical history, exposure and outcomes on exposure and outcomes captured systematically, after consent has been obtained. Like PEM and mod PEM, SCEM studies provides the opportunity to identify events that may not have been suspected as being due to the drug under surveillance. Extensions to monitor long-term safety and use is also possible.

Conclusions: By capturing data in specialist care through SCEM registries, safety data is collected on those who may be more complex in terms of underlying disease, comorbidities and concomitant medications than in the general disease population seen in PEM and Mod PEM studies and this addition to the drug safety methodology repertoire of the DSRU can meet the requirements of Risk Management Planning as part of a new paradigm in pharmacovigilance.

459. Use of Recommendations in Implementing Pharmacoepidemiology Studies for Vaccines

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Background: Several methodology guidelines have been developed to support post-authorization safety studies.Vaccines often require adapted risk management practices. A systematic review of recommendations from methodology guidelines has not been performed focused on safety studies of vaccines.

Objectives: To compare the various guidelines' recommendations for vaccines' safety studies. To assess the compliance of a selection of studies with existing recommendations. The secondary objectives were: to develop a list of methodology recommendations, to identify areas not covered by the guidelines; and to develop best practice recommendations for these areas.

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Methods: A systematic search was performed to identify guidelines referred in Pubmed, scientific publications and relevant organizations' websites. The authors of a sample of published studies,indexed in Pubmed, were contacted to obtain the protocol, the statistical analysis plan and/or the report of the studies. A framwork to review the study methodology was adapted from the STROBE Statement. Proposals for good methodological practices were developed based on examples from the analysed studies.

Results: Thirteen guidelines were selected. Of these, 552 recommendations were recorded and merged into 135 simplified recommendations. These were applied to the analyses of each study. Twenty studies were selected. The response rate from the authors was 36%. Twenty-one per cent of recommendations were assessed as "Not applicable", 45% assessed as not respected based on the available documents, and 34% assessed as respected. Five areas not directly covered by the existing guidelines concerning the methodology of vaccine studies were defined, namely: definition, ascertainment and measurement of exposure.

Conclusions: The thirteen guidelines reviewed were consistent, however the recommendations were heterogenous across documents and study types. Best practices in vaccines safety studies were proposed to complete gaps in the methodology recommendations. This methodological work contributed to enhance the quality and harmonization of methodologies to assess the benefit/risk balance of vaccines.

460. Development of the Post-Marketing Requirements (PMR) Database

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Background: Post-marketing surveillance for adverse effects has become an essential element of new drug and medical devices development in the European Union and the USA.

Objectives: The objective of this study is to present an overview of the content of a database gathering the details of Post-Marketing Requirements (PMRs), i.e., studies requested by the following regulatory agencies: European Medicines Agency (EMA, EU), the Food and Drug Administration (FDA, USA), and the Haute Autorite de Sante (HAS, France).

Methods: All drug approvals published by the EMA, the FDA, and the HAS between January 1, 2005 and December 31, 2011 were reviewed to retrieve PMRs. The information was categorized as follows: product description (brand name, INN, indication, etc.), application details, PMR details, and information source.

Results: For the FDA, we reviewed 763 original approvals and 944 supplements and included, respectively, 201 and 110 drugs approved with PMRs. For the EMA, we reviewed 349 marketing authorizations and included 38 files with PMRs. For the HAS, 3674 opinions were published in this interval with only 174 opinions with PMRs. Many requests of the HAS were long-term follow-up studies. About 43% of the PMRs requested by the FDA were pediatric studies. Actually, the EMA also requires pediatric studies but under a Pediatric Investigation Plan (PIP). Since 2005, 21 PIPs have been requested. Whatever the agency, all kinds of indications are covered by the PMRs, e.g., treatment of sepsis, asthma, malaria, depressive disorder, etc.

Conclusions: This project will be a unique source of centralized information about PMRs requested in Europe and in the US. It will be useful to observe the current trends in studies requested, to anticipate the demands, and to integrate the studies as early as possible in the product development process. The Post-Marketing Requirements database will be available online in an independent website, with access by subscription.

461. Patient's Educational Material as a Tool To Minimise Risks of Centrally Authorised Products in Europe

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Background: Risk Minimisation Measures (RMM) are pivotal to therapeutic risk management. For most medicines routine RMM are adequate to ensure their safe and effective use. However, additional RMM may be needed to manage important safety concerns. Additional RMM of Centrally Authorized Products (CAPs) in Europe are reflected as conditions or restrictions in the European Product Assessment Reports (EPAR). According to current guidance additional RMM may include educational programs to inform and guide healthcare professionals (HCP) and/or patients. However educational tools to target patients are not fully characterised. In the context of the new pharmacovigilance legislation accumulated experience was reviewed to inform guidance update.

Objectives: To describe educational tools for patients as a means of additional RMM for CAPS in Europe.

Methods: For all CAPs approved at 31/12/2011 EPARs were searched for additional RMM containing educational programs. Information was complemented with data from the European Medicines Agency databases. Two researchers reviewed independently the data for classifying educational tools targeting patients.

Results: Of 639 CAPs, 98 were approved subject to conditions, consisting of educational programs and 68/98 were subject to restricted medical prescription. Of the 98 educational programs 54 targeted only HCP; 40 were for HCP and patients, and four were only for patients. Educational tools for patients included alert card, reminder card, and

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other communication tools. For 12/44 CAPs no details of the tools used were available. For 14 CAPs alert cards were used to serve different purposes irrespectively of portability or urgency criteria and only 4/14 cards were part of labeling; reminder cards were used for five CAPs; for 13 CAPs tools included "booklet" or "patient card" to increase awareness and to guide on best actions on selected risks.

Conclusions: This review highlighted inconsistency in the use of patient's educational tools, particularly the alert card and its inclusion in the labeling. Further guidance should facilitate the selection of the most valuable approach to inform and guide patients on the safe and effective use of medicines.

462. Effectivenesss of Risk Minimisation Measures: A Review of Centrally Authorised Products in the EU

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Background: In the European Union (EU) it is a pharmacovigilance requirement to measure the effectiveness of additional risk minimisation measures (aRMM) which are imposed as a condition/restriction to Centrally Authorized Products (CAPs). This evaluation is pivotal to inform the safety specification of a product through its lifecycle and to ensure that adequate measures are adopted for its safe and effective use. However anedoctical experience at the European Medicines Agency (EMA) suggested inconsistencies and limitations in the measures of effectiveness of aRMM.

Objectives: To describe measures of effectiveness of aRMM imposed as a condition to the initial authorisation of CAPs in the EU.

Methods: We searched the European Product Assessment Report (EPAR) database for CAPs authorised between 01/01/2006 and 31/12/2010 and subject to aRMM described in the EPAR Annex 127a. Two reviewers independently assessed data from the EMA databases to describe systematically the target and frequency of aRMM, proposed measures of effectiveness, and their timing.

Results: Of the 330 CAPs authorized in 2006–2010, 50 were subject to conditions outlined in the EPAR. Additional RMM targeted healthcare professionals (HCP) and patients (34/50), only HCP (15/50) or patients (1/50). Frequency of interventions was not reported for 28 CAPs, or it was described as "at launch" or "continuously" for 16 and five CAPs, respectively. Measures of effectiveness included incidence (registry, cohort) or drug utilization studies only for six and four CAPs, respectively; physician and/or patient surveys were used for 18 CAPs and were combined with analytical studies only in 4/18 CAPs. Adverse event reporting was the only effectiveness measure described for 14 CAPs, while no measures were available for seven CAPs. Timing of assessment was missing for the majority of CAPs.

Conclusions: This review highlighted inconsistencies in the measure of aRMM effectiveness. Timing of effectiveness measures was an important missing element. The systematic monitoring of aRMM effectiveness should include an assessment of the implementation process combined with a measure of risk reduction. Further guidance appears to be warranted.

463. Validation of the Draft FDA Blueprint for Prescriber Continuing Education Program for ER/LA Opioids: An Evidence-Based Approach

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Background: Failure Mode and Effects Analysis (FMEA) is a proactive, systematic, and validated risk evaluation and program design methodology used in risk intensive industries. In this study a pharmaceutical adaptation of FMEA was used to evaluate one critical component proposed by FDA for the extended release/long-acting (ER/LA) opioids REMS.

Objectives: The draft FDA Blueprint for Prescriber Continuing Education Program for ER/LA Opioids (Blueprint) was compared to the results of an FMEA previously conducted in collaboration with a manufacturer of a new ER/LA opioid product.

Methods: The care delivery process was analyzed for failures and potential causes and interventions were selected to mitigate failures. The setting included outpatient ER/LA opioid prescribing, dispensing, administration, and monitoring.

Results: The primary outcome of the study was a comprehensive list specifying content gaps between the Blueprint and the content specified by an FMEA of the care delivery process for ER/LA opioids. Findings include:

1. Thirty-three possible content gaps were identified (i.e., content specified by FMEA but not the Blueprint). Also 16 items were considered "of indeterminate need" (i.e., content included in the Blueprint but not FMEA).
2. Sixty nine per cent of the FMEA specified that content for communications to HCPs was adequately addressed by the Blueprint. Selected examples of gaps included: assess continuum of opioid use & response, do not to write for more pills than patient may need (minimize potential for stockpiling), confirm opioids are not being prescribed by other HCPs.
3. Seventy-five per cent of the Blueprint content items were also specified by FMEA. Selected examples of content of indeterminate need included: document all evaluation/treatment plans, be aware of federal/state regulations, use prescription drug monitoring programs (PDMPs).

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Conclusions: Proactive evaluation of the Blueprint with FMEA identified content gaps that can be corrected prior to implementation of the ER/LA Opioid REMS. FMEA is a useful methodology for validating and improving the design of future REMS programs. Additional validation is being conducted using other data; the results will be available shortly.

464. Communicating Quantitative Benefit and Risk Summaries in Promotional Labeling or Print Advertising: A Literature Review

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Background: Under the Food, Drug, and Cosmetic Act, promotional materials for prescription drugs must strike a fair balance in presentation of risks and benefits.

Objectives: This literature review addressed whether addition of quantitative summaries on the benefits and risks of prescription drugs in a standardized format (e.g., a table or drug facts box) to promotional labeling or print advertising improves health care decision-making.

Methods: We used PubMed for the literature search limiting to the English language, the core clinical journals, and journals frequently publishing risk communication research. An Expert Panel provided guidance on the search strategy and suggested citations to include. Two reviewers independently reviewed the titles and abstracts for inclusion. We reviewed the full text for citations meeting the inclusion criteria to see if they communicated risk/benefit information either: (1) numerically (e.g. percent) vs. non-numerically (e.g., increased risk) or (2) numerically using different formats. Publications that met these criteria were abstracted into standardized evidence tables.

Results: We identified 674 relevant publications, of which 52 met our criteria for inclusion. Thirty-sevent of these articles focused on drugs. Presenting numeric information appears to improve understanding of risks and benefits relative to non-numeric presentation; presenting both numeric and non-numeric information when possible may be best practice. No single specific format or graphical approach emerged as consistently superior. Our review also suggested numeracy and health literacy are variables that deserve more empirical attention as moderators.

Conclusions: There are limitations of the current literature, the most important of which is tendency to use hypothetical (rather than actual) risk/benefit scenarios for drug use in people without the condition. A limitation of our review is possibly omitting some articles by only using PubMed for our search. Despite limitations, the evidence suggests that people seem to prefer numeric presentation of risk information; such presentation has been linked to greater knowledge gain and more accurate risk perceptions.

465. Abstract withdrawn by author.

466. Measurable Recommendations of Additional Risk Minimisation Measures of Medicinal Products in the EU

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Background: With the new EU pharmacovigilance legislation monitoring the outcome of risk minimisation measures (RMM) will become mandatory. It is an area that is still underdeveloped.

Objectives: To describe the recommendations of the additional RMM of centrally authorised products (CAPs) and to evaluate whether and how effects of recommendations would be measurable, in particular through use of existing observational data.

Methods: European Public Assessment Reports of CAPs were reviewed to identify key elements of the additional RMMs. Key elements were classified as: (1) measurable using routinely collected data from actual care, (2) measurable through de novo data collection or (3) not measurable. The specific type of data needed to study the compliance to the recommendations were identified for each key element.

Results: As of 1st April 2011 68 CAPs with additional RMMs were identified, which in total contained 823 key elements. One hundred eighty-one key elements (22%), which mainly included recommendations regarding prescription and patient monitoring prior to or during treatment, were considered measurable using routine care databases. Four hundred ninty-four key elements (60%) were only measurable when additional data will be collected. The majority of these key elements included information for health care professionals and patients, and instructions for patients regarding treatment use. Recommendations requiring an action of health care professionals can be monitored in routine care databases using prescription data and other clinical data i.e., laboratory values, medical diagnosis. Questionnaires and observations can be used to collect data on knowledge and behavior of health care professionals and patients.

Conclusions: Databases which reflect actual care could play a role in the rapid assessment of the effects of the

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additional RMMs. The proportion of recommendations that are measurable using routine care databases is relatively low at this moment and could be improved by formulating key elements with objectives requiring a specific action. This should be considered during the design of 'Conditions and requirements of the marketing authorization regarding safe drug use'.

467. Difference in Rates of Abuse Following Reformulation of Extended Release (ER) Oxycodone Using Data from the Radars® System Poison Center Program

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Background: In August 2010, Purdue Pharma introduced a reformulated extended release (ER) oxycodone product (ORF) that is intended to deter crushing and forms a gel when dissolved, with the goal of deterring abuse through routes that require tampering.

Objectives: This study examines whether there was a decline in rates of abuse of ER oxycodone reported to poison centers participating in the RADARS® System after introduction of ORF. Poison centers participating in the program covered 90% of the US population in the 3rd quarter of 2011.

Methods: Mentions of ER oxycodone and other prescription products (''exposures'') were obtained on a quarterly basis from participating poison centers. Intentional exposures were coded abuse or non-abuse (misuse, self-harm, withdrawal, or unknown). Rates were calculated for abuse and for non-abuse intentional exposures per 100,000 population and per 1,000 unique recipients of dispensed drug (URDD) for each year/quarter. 10/2008 through 9/2010 was considered the period before and 10/2010 to 9/2011 was considered the period after introduction of ORF. The mean abuse rates for ER oxycodone as well as other prescription opioid drugs were compared before and after introduction of ORF using negative binomial regression.

Results: There was a 34% (95% CI: 25–42%) decline in the average abuse rate of ER oxycodone per 100,000 population and 30% (95% CI: 20–38%) decline in the rate per 1,000 URDD after the introduction of ORF. These declines were greater than changes observed for other opioids excluding ER oxycodone and declines observed in ER oxycodone non-abuse rates.

Conclusions: Our results suggest that the introduction of the reformulation was followed by a decline in rates of abuse of ER oxycodone products manufactured by Purdue reported to poison centers participating in the RADARS® System. The observed decline for abuse was greater than that for other prescription opioids and that for non-abuse intentional exposures for ER oxycodone.

468. Abstract withdrawn by author.

469. Use of Recently Developed Substances as Doping in University Athletes and Risk of Adverse Reactions

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Background: Success of modern pharmaceutics, development of new pharmacological groups and medicines form background conducive to use of new agents as doping in sport. Additional unfavorable factor that influence on doping abuse in Ukraine is a lack of modern laboratories. The use of new substances in not-professional athletes, i.e., in university sport is not well studied.

Objectives: To study incidence of new substance use as doping in university athletes and to determine the concrete drugs used by them.

Methods: Two hundred twelve sportsmen which participate in team sport (football, volleyball and basketball), runners, gymnasts, boxers and wrestlers were anonymously asked about drugs they used during training and competition. We used own questionnaire focused on effects of medicine that is taken by sportsman and its side effects.

Results: We have found that 29 (13,68%) asked persons took or take a drug "to improve their professional skills". No one medicine mentioned in answers is included in the 2011 Prohibited List (International standard) of World anti-doping agency (WADA). The most frequent drug (18 cases – 8.49%) taken by sportsmen is trimetazidine that improve myocardium metabolism and increase its tolerance to hypoxia. In all cases it was chosen by athletes of team sports. Another metabolic agent thiotriasoline was used in five (2.36%) cases (four football players and one boxer). Ivabradine was mentioned in six (2.83%) answers (three boxers, two wrestlers and one runner) and silymarin - in two answers (wrestlers). Two questionnaires contain information about rash caused by thiotriasoline, 1 - about rush caused by trimetazidine and one about tachycardia due to trimetazidine use.

Conclusions: University sportsmen is high risk group of off-label use of modern medicines as doping. The use of trimetazidine, thiotriasoline, ivabradine and silymarin in athletes is not prohibited but need more detailed discussion about inclusion of them in WADA warning list or in list of prohibited substances because they may favor unfair competition and due to risk of adverse reactions be

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harmful for health. The development of laboratory tests which allows revealing of these substances in organism are also necessary.

470. A Six-Year Review of Adverse Events Related to Yunaconitine and Crassicauline A (2006–2011) in Hong Kong

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Background: Investigation on Chinese medicine related adverse events is important to protect public health. The Department of Health (DH), Hong Kong SAR, has received notifications of adverse events related to two distinctive aconitum alkaloids, yunaconitine and crassicauline A since 2006.

Objectives: To identify contributing factors to poisoning by the two alkaloids so as to inform public health control strategies.

Methods: The database of the Adverse Incident Reporting System for Chinese Medicine was retrieved. Case records related to aconitine poisoning were studied to identify distinctive epidemiological, clinical and laboratory features. Literatures were reviewed to find clue to possible herbal sources of the two alkaloids.

Results: From 2006 to 2011, DH received 26 cases notification related to yunaconitine and/or crassicauline A. No fatal case was recorded. Nineteen (73.1%) patients were female and others were male. Patients' age ranged from 13 to 78 years (median 52 years). Ten (38.5%) patients consumed the herbs for musculoskeletal complaints. All patients (100%) presented with numbness, and 13 (50.0%) suffered cardiac arrhythmia and hypotension. The onset time ranged from few minutes to 5 hours after consumption (median 1 hour). Prescriptions of all cases did not include herbs known to contain the two alkaloids. Two non-aconitine containing Chinese medicines had a high frequency of occurrence in the prescriptions. Morphological examination of the herbal remnants and/or unused herbs did not identify gross contamination by herbs containing the two alkaloids. Literature review revealed that these two alkaloids were highly toxic and found in certain species of aconitum plants originated from south-western China, which were rarely used as Chinese medicines in HKSAR.

Conclusions: Conducting active market surveillance of targeted herbs is important to identify contamination by toxic alkaloids via microscopic detection and laboratory analysis. The findings highlighted the need of enhance source control e.g., Promulgation of good agricultural and manufacturing practices etc. and encourage health care professionals in the private sector to reporting poisoning cases.

471. Severity of Adverse Drug Reactions Reported from Hospitals and Ambulatory Care Settings in Central Portugal: An Update

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Background: The prevalence of severe adverse drug reactions (ADR's) reported to the Central Portugal Regional Pharmacovigilance Unit (UFC) from 2001 to 2009 was presented in the 27th ICPE, 2011. The update of such data was found to be of importance in confirming such results.

Objectives: This study was carried out to compare the prevalence of severe ADR reported from hospitals and from primary care settings and to further assess their previous description according the medicines' SmPCs. Furthermore comparisons between the results obtained in 2009 with those of the end of 2011, with a two years length increase, were studied in order to confirm the previous findings.

Methods: ADR's reported to UFC from 2001 to 2011 were included in this study. An expert panel, comprised by experts in pharmacology, clinical pharmacy, pharmacy and medicine, assessed ADR's causality, severity and their previous description. Causality was established by global introspection method, according to the WHO criteria. ADR's previous description was assessed by consulting medicines' SmPC's. Severity was assessed according to Portuguese Pharmacovigilance System criteria. Chi square and Fischer's exact tests were applied, significant levels being set at 5%.

Results: A set of 931 spontaneous reports, corresponding to causality assessments as certain, probable or possible, was included in the study, of which 331 from hospitals. Proportion rates of severe ADR's were 70% in those from hospitals and 34% in those from primary care settings ($p < 0.05$). Rates of non-previous described ADR's were similar for both settings (14% vs. 14%, $p > 0.05$). Two years ago, for 502 cases, proportion rates of severe ADR's were 78% in those from hospital and 30% in those from ambulatory care settings ($p < 0.05$). Rates of non-previous described ADR's were 17% and 13% ($p > 0.05$) respectively.

Conclusions: These results, besides confirming that severe ADR are more likely to be reported from hospitals, are consistent with those previously presented.

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472. Ten Years of Activity of the Regional Pharmacovigilance Unit of Central Portugal and Its Contribution for Drug Safety Knowledge

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Background: Spontaneous reporting is a method of pharmacovigilance used by health professionals to report suspected ADR. Reporting suspected ADR contributes to better benefit/risk ratio evaluations of drugs and for patient safety.

Objectives: This study aims to characterize the ADR reported to the Regional Pharmacovigilance Unit of Central Portugal (UFC), to document the contribution of reports of ADR by health professionals to pharmacovigilance in Portugal, and to identify the new knowledge produced by the activity of the UFC.

Methods: Spontaneous reports (SR) of ADR received in the UFC between January 2001 and August 2011 were included. Causality was assessed using the global introspection method. Severity was assessed according to World Health Organization (WHO) criteria. Previous description of an ADR was assessed by consulting the Summary of Product Characteristics for suspected drugs. Suspected drugs were classified in categories according to the Portuguese Drug and Therapeutics Bulletin. ADR were classified according to the MedDRA dictionary. Data processing was performed using the Statistical Package for Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA).

Results: The UFC received 1,846 SR of ADR between 2001 and August 2011. Nine hundred ninty-nine met the inclusion criteria. We identified 149 (14.9%) unknown ADR and 428 (42.8%) serious ADR. Seventy (7.0%) ADR were simultaneously unknown and serious and 41 (4.1%) simultaneously unknown, serious, and certain or probable. Physicians reported 577 (57.8%) ADR, of which 340 (34.0%) were reported by family physicians. Pharmacists reported 354 (35.4%) ADR and nurses 66 (6.6%).

Conclusions: Unknown ADR (149; 14.9%), unknown and serious ADR (70; 7.0%) and unknown serious certain or probable ADR (41; 4.1%) received by the UFC show that SR is of great value in increasing knowledge about the safety profiles of drugs.

473. Factors Causing or Contributing to Adverse Drug Reactions in Hospitalized Patients

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Background: Various factors are causing or contributing to adverse drug reactions (ADRs) in hospitalized patients and in order to prevent their occurrence it is necessary to be aware and to understand the cause of the ADRs.

Objectives: The main objective of the study was to identify the factors causing or contributing to the occurrence of adverse drug reactions in hospitalized patients in Romania.

Methods: ADRs cases identified in two internal medicine departments from two clinical settings during a 2 year period were stored in a specially designed database meant for data storage and in-depth analysis and research. Causes for the ADRs occurrence were investigated at completion of the patients' chart, and by that meaning if the ADR was a consequence of a contraindication, an inadequate dose or administration frequency, a drug interaction, inappropriate prescribing decision for the patient's condition (known allergy, renal insufficiency, hepatic insufficiency, other special warnings), inadequate therapy monitoring, self-medication, non-adherence to therapy. A retrospective analysis of the ADRs cases was performed in order to determine what the causes of the registered ADRs were. Descriptive statistics was used.

Results: Two hundred and one patients experienced 251 ADRs. Out of those, 51 were caused by drug interactions, in 32 cases the drug was used disregarding the precautions, 19 inadequate dose or administration frequency, 14 inappropriate prescribing decision for the patient's condition (known allergy, renal insufficiency, hepatic insufficiency, other special warnings), 14 ADRs caused by self-medication, 10 inadequate therapy monitoring, 5 were the consequence of a contraindication, 2 ADRs due to non-adherence to therapy and 118 ADRs had other causes. It is possible for an ADR to have one or more causes.

Conclusions: More than half of the ADR cases may possibly have been avoidable (133 cases, 52.99%) and drug-drug interactions (51 cases) was the most common cause of the ADRs.

474. Medication Error: A Critical Analysis of the Recent Literature

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Background: Although "Medication error" is a well-known and widely examined problem, it is also an

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unsolved question which extent is difficult to estimate, especially if we considered that errors represent human nature and drug management is a very complex process, so errors can happen at all times.

Objectives: To investigate what is known in these last years about medication error and to evaluate hospital pharmacist's involvement in preventing and reducing medication errors.

Methods: Relevant studies published in the English language were identified by searches of Medline from 2009 to 2011.MeSH terms were medication errors, hospital pharmacy service, clinical pharmacist, risk assessment.

Results: Fifty-seven articles were included in the analysis: 12 reviews and 31 studies. The number of articles has decreased from 2009 (28) to 2011 (8). Three articles gave attention to classify medication error (slips, lapses, mistakes). Four articles considered all sorts of medication error (from prescribing to administration stage). Some articles focused on specific type of error or setting of case: prescribing (13), transcribing (1), dispensing (5) error and emergency department (4), oncology (2), intensive care unit (2). Two studies investigated attitudes of healthcare professionals in reporting medication errors: pharmacist was the professional most likely to report errors and one article underlined that he reported medication errors of all severities. An intervention study showed that pharmacist's involvement reduced prescribing errors (from 190.5 to 62.5/1,000 monitored patient-days). A review of medication-error reports showed an increase of alerts after clinical pharmacists' addition (from 31 to 371). In an observational study pharmacists intercepted or intervened in potential medication errors at a rate of 3 per 100 medications ordered.

Conclusions: The main message of all items is the prevention of errors through their early detection and immediate reporting. The information technology could be helpful to prevention errors but it was also a source of other errors. The role of clinical pharmacist in prevention and reduction of medication errors was important.

475. Development and Content Validation of a Patient-Reported Adverse Drug Event Questionnaire

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Background: Direct patient reporting of adverse drug events (ADEs) is considered important for the evaluation of the benefit-risk profile of a drug. Existing questionnaires have limited applicability because they are drug or ADE specific, not validated and/or do not ask for additional information regarding the nature of the experienced ADEs, e.g., causality assessment, duration, severity.

Objectives: To develop a generic patient-reported questionnaire to identify and quantify the nature of experienced ADEs, and test its content validity.

Methods: Based on existing questionnaires and patient reported ADE information from the Lareb Intensive Monitoring Project, a draft list was created of commonly reported ADEs in lay-terms. ADEs were classified in body categories, and mapped to the Medical Dictionary for Regulatory Activities. Questions regarding the nature of the ADE were derived from existing questionnaires and the Naranjo scale. Readability and clarity of items and response options were tested in cognitive debriefing interviews with patients who use chronic drugs for diabetes or asthma/chronic obstructive pulmonary disease. Interviews were recorded and transcribed verbatim. Identified problems were discussed by two researchers. The questionnaire was revised in an iterative process until no major problems were detected. In addition, 24 patients were asked to do a classification task, in which a random sample of ADEs was classified into body categories.

Results: The questionnaire was validated by 25 patients and revised 15 times, rephrasing questions and response options and improving lay-out. Based on the classification task, 39 changes were made regarding the grouping or labelling of ADEs in body categories. The final questionnaire contains a checklist with 252 ADEs organized in 16 body categories, and including 15 questions per reported ADE.

Conclusions: We developed a novel generic patient-reported ADE questionnaire intended for post-marketing studies and clinical trials. We confirmed its content validity regarding questions, response options, and terminology of ADEs and body categories. A web based version is currently developed. Further validation studies are planned.

476. Exposure to New Medicines Prior to Market Authorisation: Too Few Patients and Insufficient Follow-Up

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Background: Only limited numbers of patients and healthy volunteers have been studied when new medicines are authorised. Especially, experience with long-term treatment is often limited. The exact number of people involved in registration studies however, is unknown.

Objectives: To review the total number of people who had used new medicines prior to approval, with specific

attention to the extent of long-term use of products for chronic use.

Methods: A systematic review of data from the European Union's Community Register and publicly available European Public Assessment Reports was conducted. All newly approved medicines in the EU over the years 2000–2010 were identified and unique products containing new molecular entities were included. Products were categorised as chronic use, intermittent use or short-term use. Orphan drugs were considered a separate category. The total number of subjects exposed to the new medicine was extracted. For products for chronic use the number of people with long-term use (for six or twelve months) before approval was determined.

Results: A total of 200 products were identified, including 37 orphan medicines. The median total number of people studied was 1,694 (IQR: 899–3195) for non-orphan medicines and 459 (IQR: 174–915) for orphan medicines. Among non-orphan medicines 13.5% (22) had been studied in < 500 subjects, 14.1% (23) in 500–1,000 subjects, 28.8% (47) in 1000–2000 subjects, 31.9% (52) in 2,000–5,000, and 11.7% (19) in over 5,000 subjects. Safety of chronic use (for six and twelve months) was studied in < 1000 people in 47.7% (41) and 60.5% (50) of new medicines, respectively and guideline criteria were not met in almost 10% of products.

Conclusions: The number of people studied before approval is adequate, though safety is studied marginally. The current ICH E1 guideline for chronic medication requires relatively low numbers of patients studied for six months (n = 300) or twelve months (n = 100). These limits are not met in almost 10% of products. We advocate a strengthening of the demands on the minimum size of long-term clinical trials before approval for chronic medication to allow for a better risk assessment.

477. MIHARI – Medical Information for Risk Assessment Initiative Year 3

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Background: PMDA - Pharmaceuticals and Medical Devices Agency, the Japanese regulatory agency, is being in a process of reinforcing and enhancing its post-marketing safety measures as stated in its second mid-term (FY 2009–2013) plan. MIHARI project has started in PMDA since FY 2009 to develop a new safety assessment system for post-marketing drugs, which will address: (1) secure access to claims databases and electronic medical records (EMR) databases, and (2) development of methodologies for pharmacoepidemiological studies using data from such databases. The update from MIHARI in the third year is reported.

Objectives: To develop a new safety assessment system for post-marketing drugs using medical databases in Japan.

Methods: There are five steps to develop the system, which are applied to each data source. (1) Establishment of standardized EMR data accessibility with collaborative hospitals or investigation of existing domestic databases available for drug safety assessment. (2) Evaluation of each database by characterization studies, validation studies, and other pilot studies. (3) Development of methods to select appropriate study designs and statistical analysis for each characterized database. (4) Practice about real drug safety issues using the developed safety assessment system. (5) Implementation of this system.

Results: In the third year, MIHARI was at the second and the third steps described in the methods. Characterization studies using claims data including in patients only and EMR data collecting from 6 hospitals in the standardized format were performed. Validation study about four outcomes using claims and EMR data are ongoing. For development of methods, drug use study and evaluation of effect of regulatory action using two types of claims data were conducted. Another pilot study about estimation of associations between specific drug and event was conducted with the claims data to explore feasibility. Investigation about a new signal detection method using data-mining applying to the claims data has just started.

Conclusions: MIHARI is being in good progress. Accumulated findings, knowledge, and experiences from the pilot studies may contribute to establish the new safety assessment system in PMDA.

478. Development of an Educational Pharmacovigilance Program in Francophone East European Countries

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Background: Pharmacovigilance is an arm of patient care. It aims at making the best use of medicines for the treatment or prevention of disease. In any country, a well-integrated pharmacovigilance system must exist in order to collect information on adverse drug reactions (ADRs) and ultimately result in early recognition and management of potentially drug associated risks. In Romania the Spontaneous Reporting System is poor, since only 363 ADRs were reported in 2010 at the National Pharmacovigilance Centre. A previous survey regarding the Romanian physicians attitude towards voluntary reporting of ADRs found that among the most important reason for not reporting an ADR was the lack of knowledge regarding the system.

Objectives: Our objective was to support pharmacovigilance at a local and regional level according to the special needs and weaknesses of the present situation.

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Methods: Educational interventions, in close collaboration with two French regional pharmacovigilance centers, was the method proposed for supporting and fostering the pharmacovigilance activities and spontaneous reporting in Romania and Moldavia, at a regional level, to ensure pharmacovigilance delivers its full benefits.

Results: The educational program financed by the Francophone Universities Agency comprises a two level training. First level training addresses the personnel of the Drug Information Research Center and of the Pharmacology and Clinical Pharmacy Department from the University of Medicine and Pharmacy in Cluj-Napoca and from Chisinau, respectively. The training is provided by specialists from the Bordeaux and Rouen pharmacovigilance centers. Second level training addresses healthcare professionals in Cluj-Napoca and Chisinau regions and is provided by the team trained in the first level. Both levels incorporate and provide training in the identification and reporting of adverse reactions, data collection, processing and analysis.

Conclusions: The support of pharmacovigilance at a regional level should be seen as an important opportunity for the development of a comprehensive national pharmacovigilance system and as an obligatory investment in the future public health of the territory.

479. Bayesian Hierarchical Models for ADR Detection Using Different Criteria To Group the Adverse Reactions

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Background: Using spontaneous reports to detect signals of adverse drug reactions (ADRs) is vital in spite of the problems of multiple testing. Berry & Berry (2004) proposed a three level Bayesian hierarchical model (BHM) using MedDRA grouping. Although these groupings are medically based, they may not reflect terms that occur or are reported together. Prieto & Evans (2009) suggest that data driven groupings would be more useful.

Objectives: To assess the differences in results of BHMs comparing data-driven groupings (DDGs) to WHO-ART based groups; to assess their biological plausibility and their sensitivity to data changes.

Methods: WHO's "Vigibase" was used for cluster analysis to derive groupings of terms that were correlated across drugs. These groupings and those from WHO-ART were applied in a BHM to detect potential ADRs. The results were compared and the data driven clusters assessed for clinical relevance and validity. By re-clustering the ADRs with and without particular drugs, the sensitivity of the groupings to the data was also examined.

Results: DDGs were highly sensitive to inclusion/exclusion of certain drugs and different clustering techniques. Some ADRs were consistently grouped together, and although not necessarily consistent with the ART groupings, they did not lack biological plausibility. Both WHO ART groupings and two different kinds of DDGs seemed to work well in a BHM to detect known ADRs, but there were also some differences. For example, using DDGs did not flag tongue ulcerations or hiccups as potential ADRs for proton pump inhibitors, while using WHO groupings did. Although different clustering techniques produced quite different groups, they produced similar results when applied to the BHM. Estimated standard deviations of groups tended to be smaller for the DDGs suggesting a higher degree of internal correlation between ADRs.

Conclusions: Data driven clustering of ADRs seem very sensitive to what drugs and/or techniques are used. These differences in DDGs hardly changed conclusions from the BHM, but differences were seen when using WHO-ART groups. It is still unclear whether (and what) DDGs are better than standard ADR dictionaries.

480. Adverse Drug Reactions (ADRs) in Patients Treated for Colorectal Cancer: From the Oncologists to the Patients

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Background: Cancer is a public health priority. Despite different safety profiles, conventional chemotherapy drugs and new drugs, i.e., targeted therapies, cause many ADRs. Thus, treatment adaptations are often performed according to tolerance.

Objectives: To estimate the frequency and describe the characteristics of ADRs in patients treated for colorectal cancer in an oncology unit.

Methods: Patients initiating a treatment by chemotherapy with or without targeted therapy for colorectal cancer were identified prospectively from 15 Februay to 15 April 2011 in an oncology unit of a teaching hospital and retrospectively from 1 January 2009 to 31 December 2010 by means of the hospital chemotherapy management software. Data on socio-demographic characteristics, cancer, treatments and ADRs occuring during the treatment were collected from computerized medical and nursing records using a standardized form. For the prospectively included patients, data on ADRs were also collected through a self-administered questionnaire.

Results: A total of 109 patients were included in the retrospective part (717 ADRs). Gastrointestinal effects (38%), general symptoms (13%), especially asthenia, and cutaneous effects (13%) were the most frequent. According to criteria used in pharmacovigilance, 10% were severe, while

9% were classified as grade 3 or 4 according to National Cancer Institute Common Terminology Criteria for Adverse Events. In 15% of cases, the ADR led to treatment adaptations (drug stopped, dosage reduced, etc). In the prospective part (19 patients, 63 ADRs), data collected from medical and nursing records were similar to those of the retrospective part. The 41 self-administered questionnaires reported 145 ADRs with a higher proportion of moderate and severe effects according to the patients.

Conclusions: The frequency of ADRs, especially severe, was high. Reporting of ADRs differed between healthcare professionals and patients: reporting from healthcare professionals was not exhaustive but more accurate in contrast to that of patients who reported almost everything they experienced. However, the patients experience is important to know and consider to improve care and quality of life.

481. Factors Affecting the Timing of Signal Detection of Adverse Drug Reactions

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Background: Utilizing large databases of adverse event reports such as the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) is an excellent way to detect rare or unknown adverse drug events and is becoming increasingly important in pharmacovigilance.

Objectives: We investigated factors affecting the timing of signal detection by comparing variations in reporting time of known and unknown adverse drug events after initial drug release in the USA.

Methods: The Japan Pharmaceutical Information Center (JPIC) AERS, which is the FDA AERS as edited by the JPIC, was the database for adverse drug reactions. Six adverse events associated with 6 drugs were investigated: rhabdomyolysis with rosuvastatin, malignant syndrome with aripiprazole, and hypercalcemia with teriparatide as known adverse drug reactions; and severe liver injury with telithromycin, acute pancreatitis with exenatide, and suicidal behavior with varenicline as unknown adverse drug reactions at launch. Changes in the proportional reporting ratio, reporting odds ratio, and information component as indexes of signal detection were followed at 3-month intervals after drug release, and the time for detection of signals was investigated. In addition, the time lag from the onset of adverse events until report to the FDA was calculated.

Results: The time for the detection of signals after drug release in the USA was 2–10 months for known adverse drug events and 19–44 months for unknown ones. The median lag time for known and unknown adverse drug reactions was 99.0–122.5 days and 185.5–306.0 days, respectively. The lag time for unknown adverse drug reactions was longer than that for known ones ($p < 0.01$). When the FDA released advisory information on rare but potentially serious health risks of an unknown adverse drug reaction, the time lag from the onset of adverse events until report to the FDA was shorter.

Conclusions: To detect signals of adverse events as early as possible, these results suggest that immediate reporting of adverse events is very important.

482. Safety of Non-Prescription Medications: Knowledge and Attitude of Community Pharmacy Customers in Saudi Arabia

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Background: The use of prescription medications as over the counter (OTC) is an increasing and under-recognized problem that can lead to death and poisoning associated with abuse and misuse, antibiotics resistance and misuse, adverse drug reactions, drug dependence, hospitalization and drug- drug interactions.

Objectives: The objective of the study was to measure the frequency of dispensing prescription and non- prescription medications, customers' knowledge and attitude toward medication safety, measure the frequency of illegally dispensing prescription medications without a prescription in community pharmacies in Riyadh city and customers' source and access to medical information.

Methods: This prospective cross sectional study was conducted at community pharmacies in Riyadh City, Saudi Arabia. Over 4 weeks (May – June) 2011, Five pharmacy students collected 428 self administered questionnaires from customers who were buying prescription or non- prescription medications.

Results: A total of 428 patients participated in the survey. Out of 203 patients had non-prescription medications, 89 patients obtain their medications as OTC although they need prescription. The percentage of dispensing medication without prescription to the total of prescription medications is 30%. More than 66% patient knows that there should be a prescription for their prescription medications. The reason for buying medication without prescription was not avoiding the cost of doctors' visits. The source of medications information in the majority of patient 80% are doctors or pharmacists.

Conclusions: Dispensing prescription medications as OTC was inappropriate. Although knowledge and attitude of customers toward safe use of non prescription medications show safe attitude, but there were misuse and abuse and an exchange of psychiatric and other medications in large quantities. There should be control and restriction of medications including quantities dispensed and not limiting it to antibiotics only, but also medications that are in the risk of misuse by the patient.

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483. Is Spontaneous Reporting Always the Most Important Information Supporting Drug Withdrawals for Pharmacovigilance Reasons in France?

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Background: Because of design, objectives and number of included subjects, clinical studies are insufficient to assess the safety of new drugs. Sometimes, serious adverse drug reactions (ADRs) led to withdrawal of the drug from the market.

Objectives: The objective of our study was to determine the nature of scientific evidence leading to drug withdrawals for safety reasons in France (2005–2011) and compare the results to those from a previous study (1997–2004).

Methods: Drugs withdrawn from the French market due to safety reasons (2005- 2011) were identified from the website of the French Health Products Agency. Additional information from the literature and reports of Pharmacovigilance commissions allowed to classify these withdrawals according to the nature of the evidence (clinical trials [CT], case reports [CR], case-control studies [CC], cohort studies, animal studies, observational studies). We also identified the organ classes affected and type of ADRs (A or B).

Results: A total of 22 products were withdrawn from the French market within the study period. The most frequently classes of these drugs were Nervous system (7/22; 31.8%) and Alimentary tract and metabolism (6/22; 27.3%). The withdrawal rate has increased over the study period. The nature and type of the most frequently ADRs leading to drug's withdrawal were cardiovascular (10 citations), neurological (5) and hepatic, cutaneous or psychiatric (three each one). Most of the ADRs were of type A (15/22, 68%). CR (19/22; 86.4%) and CT (13/22; 59.1%) were the most frequently evidence involved. In 5/22 (23%) cases, CR were the sole evidence. Sixty-eight percent (15/22) of regulatory decisions were based on multiple sources of evidence. In only 6 cases, CC or cohort studies were involved.

Conclusions: This study reveals an increase rate of drug withdrawals in France probably explained by the "benfluorex affair". This study underlines that spontaneous reporting remains the main cause supporting drug's withdrawal for safety reason. However, its relative importance slightly decreased in comparison with 1997–2004. The importance of pharmacoepidemiological methods increases but remains low.

484. Drug Induced-aAnaphylaxis: A Decade Review of Reporting to the Portuguese Pharmacovigilance Authority

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Background: Anaphylaxis is a potentially fatal systemic Adverse Drug Reaction (ADR). It is classified as a type-B reaction as it is an unpredictable and mostly dose-independent event that occurs suddenly after contact with the causative drug.

Objectives: Our objective was to characterize a case series of anaphylactic reactions reported to the Portuguese Pharmacovigilance authority during the past decade. Demographic data of the patients and implicated drugs were analyzed as well as severity and time trends.

Methods: Retrospective analysis of every episode of anaphylaxis, defined according to the *second symposium on the definition and management of anaphylaxis criteria*, reported to the Portuguese Pharmacovigilance System between 01/01/2000 and 01/11/2010. Report sources are health-care professionals and marketing authorization holders.

Results: Amongst a total 16.157 ADR cases declared, we found 918 cases of anaphylaxis that met the proposed criteria. Age of the patients at the episode varied from 7 days to 91 years (mean: 48 years, SD: 21 years) with 87 cases (9%) under 18 years. There is an overall female predominance (67% women) but male were predominant in pediatric ages (56%). There was a trend in increasing reporting and 31% (284) of the cases were reported during the last 2 years (2009–2010). Ninteen per cent of the episodes led to hospitalization and we found 24 (3%) cases with a fatal outcome (including four antibiotics, four antineoplastic drugs, three NSAIDs). Antibiotics were the group responsible for most cases (17%) followed by NSAIDs/Acetaminophen (13%), antineoplastic/cytotoxic drugs and immune-modulators, this group with an important increase in the last 3 years. Vaccines and radiographic contrast media were also important contributors with 60 and 40 reports respectively.

Conclusions: In this series of drug related anaphylaxis we found as other authors that most of the reported episodes were associated with widely used drugs (sometimes over the counter) as antibiotics and analgesics. Anaphylaxis can occur at any age. The female gender was more represented except for pediatric patients.

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485. Adverse Drug Reactions Resulting from Self-Medication – Evidence from Germany

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Background: Adverse drug reactions (ADRs) are known to be an important economic and public health burden, and self-medication may further contribute to it, although there are only very few quantitative analyses. In our analysis self-medication includes OTC drugs and self-administration of previously prescribed drugs.

Objectives: First, to analyze the proportion of ADRs caused by self-medication drugs and leading to hospitalization in departments of internal medicine in Germany. Secondly, to assess the ADRs and causative drugs.

Methods: Since 1996 ADR-related hospital admissions were assessed in four hospitals within the German Net of Regional Pharmacovigilance Centers. Patients hospitalized due to an at least "possible" ADR from October 1996 through to December 2007 were analyzed.

Results: Out of all patients (n = 7,558), 327 patients (4.3%; mean age 57.1 years; SD 19.2) suffering from 339 ADRs (type A 79.1%; type B 17.7%) were hospitalized due to an ADR (15.0% required intensive medical care; 0.6% caused permanent harm) that resulted from self-medication. In total, 266 (78.5%) ADRs were classified as "recovered" and one person died (GI haemorrhage caused by ibuprofen (self-medication) and prescribed phenprocoumon). System organ classes mostly affected were gastrointestinal disorders (63.4%), e.g., GI haemorrhage mainly due to acetylsalicylic acid (high-dose) or diclofenac, and the immune system (9.7%), e.g., hypersensitivity reactions mainly caused by diclofenac or metamizole sodium. In total, 56.6% of these patients (n = 327) were hospitalized caused by an ADR resulting from one suspected self-medication drug, the ADRs of 9.2% of patients were caused by drug-drug interactions (DDI) of at least 2 self-medication drugs, and 34.2% were admitted due to ADRs resulting from a DDI between self-medication and prescribed drugs.

Conclusions: The proportion of self-medication ADR-related hospitalizations seems to be quite low. Whereas two-thirds of all ADRs were caused mainly by the patient ("self-medication only" ADRs), one third of ADRs (concurrent intake of self-medication and prescribed drugs) could be influenced directly by physicians' taking a detailed drug history prior to issuing a prescription.

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488. Survey in a Sample of Italian Hospitals on Patient Safety

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Background: Recommendation no. seven of Italian Ministry of Health aims at preventing medication error. The 2011 edition of survey of implementing Recommendation no. seven comes from collaboration between Italian Society of Hospital Pharmacy (SIFO) and Ministry of Health.

Objectives: To evaluate hospital patient safety in compliance with Recommendation no. seven and to facilitate the implementation of this Recommendation through detection of difficulties related to its enforcement.

Methods: A questionnaire on drug management was compiled by pharmacist in collaboration with other health professionals.

The questionnaire consisted of three sections:

1. General information on hospitals and on knowledge of Recommendation
2. Information on drug management in pharmacy
3. Information on four phases of drug management (prescribing, transcribing, preparing and administrating) in five wards (medicine, surgery, orthopedics, pediatrics, midwifery-gynecology).

Results: Fifty-nine hospitals of 15 Regions and 269 wards participated in survey. The main results were:

General information: Almost all centers (about 90%) adopted strategies to prevent medication errors; 51% of centers scarcely know the Ministerial Recommendation

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and 90% had difficulties in its implementing mostly due to lack of resources (20) or poor involvement of health personnel (19).

Survey in pharmacy: Only 16 pharmacies always considered safety standards in purchase contracts and almost all pharmacies (58) had a controlled dispensation of electrolytic concentrate solutions. Thirty-one hospitals had computerized prescription, and 37 had the infusion therapy centralized in pharmacy.

Survey in department: Most of wards (205/269) had multidose bottles already opened or reconstituted, and often (46%) has not reported the new expiration date on the label. Labels of infusion solutions were lacking in some important information as patient's identity, name of drug, time of administration.

Conclusions: The survey documented that patient safety and prevention of medication errors is a significant problem in hospital. The management of the drug has many problems and the ministerial recommendation is poorly understood and still less applied.

489. FDA AERS and WHO Vigibase Yielded Different Results in Disproportionality Analysis for Propylthiouracil

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Background: Disproportionality analysis, based on the ratio of the observed/expected reporting proportion, is widely used in signal detection. The proportion of serious cases is approximately 60% in FDA Adverse Event Reporting System (AERS), compared to approximately 10% in WHO Vigibase (CIOMS VIII), suggesting non-serious cases, which contribute to the denominator in calculating reporting proportion, may be captured less often in AERS.

Objectives: To study whether differences in reporting proportion affect the disproportionality measures.

Methods: All postmarketing cases suspected to be associated with propylthiouracil, a first-line drug to treat Grave's disease, were retrieved in AERS and Vigibase through 30 September2011 via Qscan®-FDA and Qscan®-World. Postmarketing cases for all drugs other than propylthiouracil (background) were also retrieved separately. Disproportionality analysis was conducted for propylthiouracil vs. background. For hepatic events with identical preferred terms (PTs) and ≥3 cases in both databases, case-based reporting proportions and disproportionality measures were reviewed.

Results: A total of 808 and 2347 cases were retrieved from AERS and Vigibase, respectively, with 143 (18%) and 321 (14%) cases from hepatobiliary disorders. Seven hepatic PTs had ≥3 cases in both databases. Among them, some reporting proportions for propylthiouracil and background were strikingly different between AERS and Vigibase. In AERS, five out of seven PTs had lower 95% confidence bounds of the empirical Bayesian geometric mean (EB05) ≥2.0, whilst in Vigibase 6 out of 7 PTs had EB05 ≥2.0. Four events had EB05 ≥2.0 in both databases, suggesting a disagreement of 3/7, with the absolute difference in EB05 for these PTs averaging 2.1. Similar results were obtained when using the lower 95% confidence bound of the information component (IC05).

Conclusions: For identical events associated with the same drug, disproportionality measures produced different results in AERS and Vigibase, probably due to dissimilar reporting proportions, which may affect data interpretation in signal detection. Caution is warranted when conducting a disproportionality analysis using a spontaneous reporting database.

490. Grouping Related Medical Terms May Not Expedite Detection of Disproportional Reporting Patterns in Pharmacovigilance

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Background: A variety of terms in standard medical terminologies can be used to describe the same medical condition. Grouping related terms could expedite the detection of disproportional reporting patterns in pharmacovigilance.

Objectives: Determine to what extent grouping medical terms may expedite detection of historical safety signals.

Methods: Trifiro et al (Drug Safety, 2009) identified 13 medical concepts as important to monitor in drug safety and with medium to high probability of being drug-related. We selected MedDRA High-Level Terms (HLT), Standardized MedDRA Queries (SMQ), and (groups of) preferred terms (PT) relevant to each of those. Fourty-three historical EMA labeling changes related to these medical concepts were extracted from a reference set previously published by Alvarez et al (Drug Safety, 2010). For each level of the hierarchy along with customized groups of the identified PTs, we determined the point in time at which any Statistic of Disproportionate Reporting (IC025 > 0) related to that medical concept would have first been detected in the WHO Global Individual Case Safety Reports Database, VigiBase.

Results: Analysis at the level of individual PTs detected 25 of the EMA labeling changes in total, of which 8 were found earlier than by using HLTs, 11 earlier than SMQs, and nine earlier than customized groups. Use of PTs highlighted 6 labeling changes later than HLTs, fivelater than SMQs, and 10 later than customized groups. Ten of the 43 labeling changes pertained to the medical concept Bullous eruptions for which analysis at the level of individual

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PTs performed relatively well, which influences the overall results.

Conclusions: Our study showed limited net gain by replacing an analysis at the PT-level with one at a higher level. This may reflect that important distinctions remain between PTs associated with the same medical condition. Alternatively, it may be due to the multiple comparisons inherent in considering related PTs separately, in which case the major benefit of grouping would be better protection against spurious associations. Parallel analyses at different terminological levels would improve timeliness but have resource implications.

491. Performance of Observational Screening by System Organ Class

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Background: There has been a recent increase in interest exploring the use of observational data for post-marketing safety surveillance. In January 2011, the Observational Medical Outcomes Partnership (OMOP) reported research results which highlighted the variability found across databases, methods, and outcomes definitions. Because of the inherent nature of observational data, one would also expect variability in performance across a wide range of medical conditions.

Objectives: The objective of this research project was to evaluate the performance of observational screening across a wide spectrum of medical conditions.

Methods: Ten drugs representing a diverse range of indications and route/duration of administrations were chosen. The US package insert for each drug was used to determine true and false positives. For each drug chosen, data mining scores were generated for all drug-condition pairs in one US claims and one electronic health records (EHR) database. A statistical threshold (LB 95% CI >1 in both databases) was used to determine if the drug-condition pair was a signal. For each drug; PPV, NPV, sensitivity, and specificity were calculated. The results were stratified by MedDRA System Organ Class (SOC). As a point of reference, the same analysis was performed on AERS data using the MGPS methodology and a commonly used statistical threshold (EB05 $>$ 2).

Results: The overall performance of observational screening was a PPV of 0.11, NPV of 0.79, sensitivity of 0.15, and a specificity of 0.73. For reference, the performance of the AERS data was a PPV of 0.24, NPV of 0.82, sensitivity of 0.09, and a specificity of 0.94. When stratifying by SOC, results varied with observational screening having a superior sensitivity for 17 SOCs, AERS for three SOCs, and results for seven SOCs were indeterminate. With regards to specificity, the AERS data generally outperformed observational screening across all 27 SOCs.

Conclusions: Observational data offers the potential to improve signal detection activities, but with improved sensitivity comes a decrease in specificity. Additional research is needed in order to maximize the benefits which may be found in the analysis of observational data.

492. Practical Implications of a 0-Day vs. 30-Day Persistence Window on Datamining Observational Data

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Background: Several different methods of using observational data for signal detection advocate the use of a common data model (CDM). One issue the CDM attempt to address is that a continuous drug exposure may be represented by multiple prescriptions and a disease episode may be represented with multiple instances of the same diagnoses code. A common way to address this issue is with a persistence window (PW), a brief period of time within which similar codes are aggregated. Although the use of a PW can help to overcome the coding issues described above, practical implications on signal detection have not been evaluated.

Objectives: The objective of this research project was to evaluate the practical implications of using no persistence window (0 day PW) vs. a 30-day persistence window (30d PW) on signal detection.

Methods: A wide range of drug and condition types were chosen. Two versions of an EHR and a Claims database were created using a CDM; one with a 0d PW and one with a 30 day PW. Various metrics were calculated, including the number of occurrences of each condition, a ratio of the crude condition incidence rate for exposed patients compared to the database background rate (SRR), and the SRR confidence interval (LB95, UB95). Additionally, the number of conditions that crossed a predetermined statistical threshold based on the LB95 was evaluated. Results were compared, and the average difference in the number of condition occurrences, the LB95, the SRR, and number of conditions crossing the statistical threshold were calculated.

Results: The 30 day PW produced an average of 16.3% fewer condition occurrences; however, the average SRR and LB95 were 16.4% higher. Because of the increase in SRR and LB95, the 30d PW resulted in an average 25.6% increase in the number of conditions crossing the predetermined threshold. The results seemed to be most pronounced in drugs that are typically used chronically and conditions that have a short to medium durations.

Conclusions: For practical purposes, using a 0dPW will increase the number of condition occurrences counted but

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will generally result in lower rates and fewer signals identified when using a predefined statistical threshold.

493. Speed of Detection of Adverse Events in Spontaneous Adverse Event Databases Compared with Epidemiological Studies: Two Related Cases

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Background: The risk of bradycardia and its consequences from use of cholinesterase inhibitors (ChI) in dementia were reported in epidemiological studies in 2009 and from a case series for memantine in 2008.

Objectives: To compare the detection and timing of these associations between disproportionality analysis and published epidemiological studies.

Methods: We conducted (1) a systematic review of the literature to identify epidemiological studies reporting AEs in patients taking currently prescribed ChI and memantine, and (2) an analysis in the FDA spontaneous Adverse Event Reporting System database (AERS) using the Empirical Bayesian Geometric Mean (EBGM) statistic and 90% credibility intervals (90%CI), to allow for low frequencies of drug-event pairs. A composite event consisted of any of the following: bradycardia, bradyarrythmia, pacemaker insertion, complete atrio-ventricular block and hip and femoral fracture. AEs from all drugs in AERS was the comparator.

Results: A total of 246 cases suspected of being associated with ChI and the composite event were identified. A statistically strong signal of disproportionate reporting, adjusted for age, sex and year was observed (EBGM of 6.58, 90%CI: 5.79–7.47). Cumulative yearly analyses revealed that the signal became statistically strong in 1997, one year after approval of the first currently used ChI. The first signal was reported in an epidemiological study in 2009. For memantine, 69 suspected cases were identified with the composite event. A statistically strong signal of disproportionate reporting, adjusted for age, sex and year, was observed (EBGM of 1.87; 90%CI: 1.47 to 2–38). Cumulative yearly analyses revealed that the signal became statistically strong and stable two years after the first reported composite event. No epidemiological studies have yet been published.

Conclusions: Analysis of suspected events can be followed over time and may detect, strengthen or weaken drug-event signals much earlier than epidemiological studies.

494. Challenges in Calculating Rate Ratios of Treatment-Associated Adverse Events after Changes in Therapy in Observational Studies

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Background: Quantifying the association of a particular therapy with the occurrence of an adverse event (AE) can pose unique challenges in observational studies. When treatment is not mandated, patients may have mid-course therapy changes, and different therapies can have different half-lives (HLs). If an AE occurs at a point in time when the treatment period of a newly started medication overlaps with the HL of the halted therapy (exposure overlap period; EOP), ambiguity exists with respect to which therapy the AE should be attributed and also the corresponding time at risk (t_R), affecting both the numerator and denominator of the incidence rates.

Objectives: To determine how robust or sensitive estimated rate ratios (RRs) are in the presence of AEs that cannot be definitely assigned to a single therapy.

Methods: Data were simulated for 5,000 patients, half starting with Treatment A (TxA) and half with Treatment B (TxB). Patients were followed for 730 days with the time on first therapy modeled as a random exponential distribution (RE), allowing for the possibility of therapy change. AE occurrence was also modeled as RE such that AE prevalence was 10% for time on TxA and 25% for time on TxB. The proportions of events in the EOP (P_{EOP}) were varied, and four different methodological approaches were implemented for assigning events and corresponding t_R in the EOP. Poisson regression was employed to calculate RRs between treatments.

Results: The RR (ref: TxA) was 2.07 when no events occurred in the EOP. For cases where P_{EOP} were 1%, 3%, and 10%, respectively, the RRs were 2.04, 2.02, and 1.85 when AEs and t_R in the EOP were assigned only to the second therapy; 2.04, 2.07, and 2.11 when assigned only to the first therapy; 1.94, 1.89, and 1.74 when assigned completely to both therapies; and 2.00, 1.99, and 1.89 when assigned as half to each therapy.

Conclusions: RR estimates appear to be biased towards the null when AEs in the EOP are assigned to both treatments even when the proportions of AEs in the EOP are relatively small.

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495. Signal Detection on Spontaneous Reports: A Comparison of the Performance of a Method Based on Disproportionality and a Method Based on the Time from Immunisation to Onset of Adverse Events

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Background: Disproportionality (DP) methods measure how unexpected the observed number of adverse events is after a specific immunisation. In contrast, time-to-onset (TTO) methods measure how different the TTO distribution of a vaccine-event pair is compared to what would be expected from the other vaccines and events. TTO and DP methods are complementary both in their methodology and in their limitations.

Objectives: To compare the performance associated with each method for each parameter choice.

Methods: For the disproportionality models we tested 176 different combinations of stratification factors (Sex, Age, Region and Year) and threshold values of a Multi-Item Gamma Poisson Shrinker (MGPS). For the TTO models we tested 18 different combinations of levels of significance and lengths of time windows for the two-sample Kolmogorov Smirnov (KS) tests. Spontaneous data from eight vaccines were used along with their associated product labels as a proxy for true positive safety signals. For each vaccine, models were ranked according to the Positive Predicted Value (PPV) and a median rank across vaccines was attributed to each model.

Results: The model with the highest median rank was a TTO model with a significance level of 0.01 for the KS tests and a time window of 60 days post immunisation. The models with the next 14 highest median ranks were all TTO models with different significance levels and different time windows (30, 60 or 90 days). The highest ranked MGPS model came up only at the 16th position for the model stratified by Sex, Age, Region and Year with a threshold value of 0.8. The median ratio of the PPV associated with the best TTO over the best MGPS model was 2.5.

Conclusions: For the eight vaccines studied, signals found by the majority of the TTO models presented a higher proportion of true positive signals than for any MGPS model. Considering the complementarity of both signal detection methods it is suggested to use both methods in parallel.

496. Characterisation of Databases (DBs) Used for Signal Detection (SD): Results of a Survey of IMI PROTECT Work Package (WP) 3 Participants

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Background: The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency (EMA). WP3 includes assessment of SD methods applied to DBs of spontaneous ADRs. Partners surveyed include three national regulatory agencies (RAs), three pharmaceutical companies (PCs), the EMA and the Uppsala Monitoring Centre (UMC).

Objectives: To describe different spontaneous report DBs with regard to size and content as context for future assessment of the relative performance of SD and duplicate detection methods in these DBs.

Methods: The survey, completed online, comprised five sections: (1) general information including types of therapeutic agent, coding dictionaries, use of meta data and signal and duplicate detection algorithms; (2) counts including those based on seriousness, reporter type, country of origin, therapeutic agents and events; (3) data elements including presence of demographic data and drug details; (4) database coverage in terms of predominant drugs and events (5) vaccine specific information. Data were summarised descriptively.

Results: Data from the 8 respondents were obtained between September 2010 and Aug 2011. DB size varies greatly (range 69,000–5,391,000 spontaneous reports). DBs are comparable in terms of: proportion of serious to non-serious reports; country of origin; predominant body systems to which events are coded; availability and completeness of certain data elements such as gender, age and country of case. There is little comparability in SD algorithms employed or use of meta-data (e.g., flags for targeted, designated or important medical events). Predominant drugs and drug-event pairs vary and appear to reflect historic parochial issues. Annual report numbers continue to rise in PC, EMA and UMC DBs. The pattern of reporters, particularly in PC DBs, has changed over time.

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Conclusions: The heterogeneity of spontaneous DBs is likely to be an important consideration when assessing the performance of SD algorithms in future studies.

497. A Network Meta-Analysis of Antibiotics for Treatment of Hospitalized Patients with Suspected or Proven Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infection

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Background: Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) pose a serious health risk.

Objectives: To use a novel method for assessing comparative effectiveness and safety of parenteral antibiotics for complicated skin and soft-tissue infections (cSSTI) and hospital-acquired or ventilator-associated pneumonia (HAP/VAP).

Methods: We did a systematic review, searching electronic databases including the archives of FDA/CDER, and performed a Bayesian network meta-analysis (MA) to simultaneously compare antibiotics and rank them on efficacy, defined as clinical success in the modified intention-to-treat population (MITT) and in the MITT population with MRSA at baseline, on all-cause mortality (in pneumonia), serious adverse events, and withdrawals due to adverse events. Models adjusted for clinical heterogeneity between studies.

Results: We identified 24 randomized controlled trials (RCTs) that compared one of five antibiotics to vancomycin. For cSSTI (17 RCTs), linezolid and ceftaroline were the most effective antibiotics, as indicated by the ranking for clinical success. For HAP/VAP (10 RCTs), linezolid ranked better than vancomycin. Safety results generally mirrored efficacy findings. Although direct pairwise meta-analysis of the RCTs generally found no statistically significant differences between vancomycin and its comparators, the network MA indicated that vancomycin ranked third (of six) in cSSTI and second (of four) in pneumonia on both efficacy and safety. Adjustment for between-study variability in diabetes (for cSSTI) and presence of VAP (for pneumonia) did not change efficacy result interpretation. Performance and detection bias were likely present in cSSTI trials involving linezolid, but regression methods could not adjust for this potential bias.

Conclusions: In these RCTs the preferred agents were ceftaroline (for cSSTI, not studied in HAP/VAP) and linezolid. Translation of these findings into practice should consider the small size of the evidence networks and the consequent uncertainty associated with the parameter estimates, the lack of evidence for ceftaroline in patients with severe renal impairment, and the lower internal validity of some of the linezolid trials.

498. Abstract withdrawn by author.

499. Comparative Effectiveness of First Line Therapy for HIV Infection: Proven Clinical Benefit over 10 Years

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Background: Randomized clinical trials (RCT) of combination antiretroviral therapy (cART) have informed the use of specific antiretrovirals and their combination for optimizing therapeutic efficacy.

Objectives: Using the UNC CFAR HIV Clinical Cohort (UCHCC), we assessed the effectiveness of provided cART in clinical care across time in response to new knowledge obtained via RCTs.

Methods: We included all patients participating in the UCHCC initiating cART between 2000 and 2010. Primary outcomes were HIV RNA level and change in CD4 cell count at 12 months following cART initiation. We used intention to continue treatment, missing equals failure (HIV RNA) and last observation carried forward (CD4) for patients lost to care. To evaluate changes in the proportion of patients with suppressed HIV RNA(<400 copies/mL) and improved CD4 cell counts(>100 cells/μL) over time we used logistic regression models adjusted for available baseline characteristics (sex, race, age, transmission risk type, HIV RNA, CD4) to calculate average per year percentage increase and associated 95% confidence intervals (CI).

Results: Between 2000 and 2010, 1,070 UCHCC patients initiated cART. Patients were 72% male and 57% black. Median age at cART initiation was 36(IQR:29, 44), CD4 count was 231(IQR:64,397) and HIV RNA was 4.5 (IQR:3.2, 5.2). Initial cART regimens changed across time with more patients initiating ritonavir-boosted protease inhibitors in more recent calendar years ($p < 0.05$). In 2000, the proportion of treated patients with suppressed HIV RNA at 12 months was 53% compared to 88% in 2010. The proportion of treated patients with a >100 increase in CD4 cell count at 12 months was 43% in 2000 and 70% in 2010. Adjusted for baseline covariates, the

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average per year percentage increase in the proportion of patients with HIV RNA suppression and improved CD4 cell counts were 5.6% (95% CI:5.5–5.7%) and 5.4% (95% CI:5.3%–5.5%).

Conclusions: Our results demonstrate improvement of cART effectiveness over the last decade. Large well-conducted clinical cohort studies such as the UCHCC provide the ability to evaluate the translation and dissemination of new clinical knowledge from RCTs to HIV clinical care.

500. Comparative Effectiveness of First Step Antihypertensives and Risk of Cardiovascular Outcomes in Older Adults

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Background: In older adults it is unclear which drug classes have an impact in reducing cardiovascular disease (CVD) associated morbidity and mortality due to age/gender effects and differences in comorbidities.

Objectives: To estimate the effect of initiation of antihypertensive medication on mortality and risk of cardiovascular outcomes, among older adults with risk factors for CVD.

Methods: Retrospective cohort study of Medicare beneficiaries (2006–2009), ≥65 years, at high risk for CVD, initiating an antihypertensive after at least 6 months without use, and with ≥1 year of continuous enrollment prior to the date of therapy initiation (index date). Exposure was defined as initiation of thiazide-type diuretics (THZ), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin II receptor blockers (ARB). Primary outcomes were all-cause mortality, non-fatal MI and stroke. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression in an "intent-to-treat" approach. Inverse probability of treatment weights were used to account for differences in age, sex, race and comorbidities, by weighting each new user of ACEI, CCB or ARB to the covariate distributions observed among THZ initiators.

Results: Of 140,461 new users, 9,605 (6.8%) died during follow-up, 496 (0.4%) had a non-fatal MI and 2,377 (1.7%) had a stroke. Relative to THZ users, the risk of death was higher among new users of CCBs (HR 1.14, CI: 1.06–1.24) and lower among new users of ARBs (HR 0.84, CI: 0.77, 0.92). New users of CCBs had a 22% higher risk of stroke (HR 1.22, CI: 1.04, 1.42). The risk of non-fatal MI was higher among new users of ACEIs (HR = 1.43, CI: 0.99, 2.06; p = 0.057).

Conclusions: Preliminary results indicate potentially important differences in the risk of mortality, non-fatal MI, and stroke among new users of antihypertensives. We are currently exploring the effects of treatment contrary to indication, duration of initial therapy, as well as augmentation and switching patterns in this setting.

501. Evidence Based Drug Therapy and Medium-Long-Term Outcomes in Very Old Patients after Acute Myocardial Infarction

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Background: Evidence on real-life effectiveness of secondary prevention after myocardial infarction (MI) in very old patients is scarce.

Objectives: The aim of this study was to measure survival and incidence of new MI in a cohort of very old patients and to estimate the association with adherence to guideline-recommended drug therapy.

Methods: From the Regional Hospital Information System we identified all acute MI patients aged 80+ years, resident in the Lazio Region in 2006–2007. Patients were linked with Regional Drug Register and Mortality Register. Antiplatelets, Beta-blockers, Agents acting on the renin-angiotensin system and Statins were identified (ATC classification). For each drug group, exposure was defined as proportion of days covered ≥75%. Outcomes were overall mortality and re-infarction during a follow-up ranging from 2 to 4 years. Two separate nested case-control studies were performed, matching four controls to each case, by gender, age and individual follow-up. We used a conditional logistic regression model and potential confounders, were selected through a bootstrap stepwise procedure.

Results: One thousand two hundred twenty-six patients with MI were studied, 58.2% females, mean age 84 years among males and 85 among females. Drugs most frequently used were antiplatelets (54.9%) and ACE-inhibitors/Sartans (53.8%).Overall, mortality was 169.3, re-infarction 117.9 for 1,000 p-year. Exposure to drugs was associated with reduced mortality: antiplatelets (OR_{adj} = 0.92, p-value = 0.51), beta-blockers (OR_{adj} = 0.92, p-value = 0.74), agents acting on the renin-angiotensin system (OR_{adj} = 0.94, p-value = 0.59) statistically significant only for statins (OR_{adj} = 0.77, p-value = 0.04). The same pattern was observed for re-infarction, with statins and antiplatelets reducing the risk significantly (OR_{adj} = 0.72, p-value = 0.03; OR_{adj} = 0.71, p-value = 0.03, respectively).

Conclusions: Observational studies using routinely collected databases offer a good opportunity to evaluate groups of population that are often under-represented or excluded from clinical trials, like elderly or those with comorbidities.

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502. Comparative Effectiveness of Losartan vs. Candesartan in Patients with Heart Failure

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Background: The benefit of angiotensin receptor blockers (ARBs) in heart failure (HF) is generally regarded as a class effect, but no head-to-head randomized trials have compared individual ARBs. Results from observational studies suggest that losartan may be associated with increased mortality in patients with HF compared to other ARBs.

Objectives: To assess the hypothesis that losartan use is associated with increased all-cause mortality in HF-patients as compared to candesartan.

Methods: We conducted a comparative study using nationwide Danish registries, with individual-level information on hospital contacts, filled prescriptions and potential confounders. Patients aged ≥45 years with first-time hospitalization for HF in 1998–2008 were identified from the Danish National Patient Registry. Among these, new users of losartan and candesartan were selected for inclusion in the study cohort. We used Cox proportional-hazards regression to compare the risk of all-cause mortality in users of losartan and candesartan.

Results: Among users of losartan (n = 4397), 1,212 deaths occurred during 11,347 person-years of follow-up compared to 330 deaths during 3,675 person-years among users of candesartan (n = 2,082). Compared to candesartan, losartan was not associated with increased all-cause mortality (adjusted hazard ratio [HR] 1.10, 95% CI 0.96–1.25) or cardiovascular mortality (HR 1.14, 95% CI 0.96–1.36). Compared to high doses of candesartan, low- (HR 2.76, 95% CI 2.16–3.53) and medium dose losartan (HR 1.37, 95% CI 1.09–1.72) was associated with increased mortality; use of high-dose losartan was not (HR 0.70, 95% CI 0.49–0.99).

Conclusions: This large nationwide cohort study of patients with HF found no significantly increased risk of all-cause mortality associated with overall use of losartan as compared to candesartan. Although low doses of losartan were associated with increased mortality, there was no increased mortality comparing high dose losartan against the highest doses of candesartan. This supports that losartan is comparable to candesartan in equivalent doses.

503. Adherence to Antihypertensive Agents after a Recent Ischemic Stroke and Risk of Cardiovascular Outcomes

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Background: Antihypertensive agents have been shown to reduce the risk of major cardiovascular events. However, there are no large effectiveness studies which have assessed adherence to antihypertensive medications and major cardiovascular outcomes in high risk individuals who have recently suffered an ischemic stroke.

Objectives: Our primary aim was to evaluate the relationship between antihypertensive drug adherence and non-fatal vascular events in a cohort of older patients hospitalized for an ischemic stroke and discharged in the community.

Methods: A cohort of 14,227 patients with an ischemic stroke was reconstructed from individuals 65 years and older who were treated with antihypertensive agents between 1999 and 2007. A nested case-control design was conducted to evaluate the occurrence of non-fatal major cardiovascular outcomes including stroke or myocardial infarction. Every case was matched by age and duration of follow-up with up to 15 randomly selected controls. The adherence to antihypertensive drugs was measured with the medication possession ratio. Conditional logistic regression models were performed to estimate the rate ratio of non-fatal vascular events associated with adherence to antihypertensive agents, adjusting for various potential confounders.

Results: Mean patient age was 75 years, 54% were male, 23% had diabetes, 47% dyslipidemia, 38% coronary artery disease, and 14% atrial fibrillation or flutter. Adherence to antihypertensive therapy of ≥80% decreased the risk of non-fatal vascular events RR: 0.74 (0.67–0.83), compared to an adherence of <80%. A reduction in all cause mortality RR: 0.52 (0.47–0.58) was also associated with higher adherence. Male gender and cardiovascular disease were also risk factors for non-fatal vascular events.

Conclusions: Our study suggests that higher adherence to antihypertensive medication is associated with a risk reduction of non-fatal vascular events and all-cause mortality among patients with a recent ischemic stroke.

504. Comparative Evaluation of Short-Term Risk of Cardiovascular Events with Antidiabetic Step-Up Therapies among Older Adults

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Background: In type 2 diabetes (T2D) patients, comparative effectiveness of second line drugs to reduce cardiovascular (CV) risk is controversial.

Objectives: We compared the risk of adverse CV outcomes after initiating step-up therapy with sulfonylureas (SU), thiazolidinediones (TZD) and DPP4 inhibitors (DPPI) in T2D patients using metformin (MET).

Methods: We conducted a retrospective cohort study using 2006–2009 Medicare (Part A,B,D) data. The study

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population was T2D patients age > 65 years on MET monotherapy who initiated step-up therapy with SU, TZD or DPPI. Patients had to be continuously enrolled in the pre-index year and fill at least one MET script in the 6 months pre-index. After initiating step-up therapy, patients had to fill another script of the same drug within 3 months and follow-up started from the second fill date. To ensure augmentation, patients had to fill a MET script between two scripts of the new drug. Primary outcome was nonfatal acute myocardial infarction (MI) and secondary outcomes were CHD(combined MI, unstable angina, CABG, PCI) and stroke. In an intent to treat analysis, we used multivariable Cox proportional models to estimate hazard ratios and 95% confidence intervals(CI) adjusted for pre-index drug use (6 months) and comorbidities including CV disease, diabetes complications (1 year).

Results: Twenty two thousand one hundred ninety-seven augmenters with mean age 73 years initiated SU (60.8%), TZD (24.4%) or DPPI (14.8%) therapy. During 408 days of median follow-up, there were 294 MIs and 4,817 secondary outcomes. Relative to SU, augmentation with DPPI was associated with a decreased hazard of MI (adjusted HR = 0.70 CI:0.51–0.96) and augmentation with TZD was associated with a more modest reduction in the MI hazard (adjusted HR = 0.84 CI:0.65–1.08). No difference in the hazard of secondary outcomes was seen with TZD (adjusted HR = 0.99 CI:0.94–1.06) or DPPI (adjusted HR = 0.97 CI:0.90–1.05) compared to SU.

Conclusions: Preliminary results indicate decreased short-term MI risk when T2D patients augment MET with DPPI or TZD compared to SU. Additional data controlling for time-dependent covariates and distinguishing the effect of drugs within the TZD class will be presented.

505. Comparative Effectiveness of Dipeptidyl Peptidase-4 Inhibitor for the Risk of Cardiovascular and Cerebrovascular Disease in Patients with Type 2 Diabetes

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Background: The risk of cardio- ? cerebrovascular (CV) disease in users of hypoglycemic agents must be quantified to permit reasoned therapeutic choices.

Objectives: To compare the risk of CV disease in patients with type 2 diabetes who began dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin therapy vs. those who began sulfonylurea (SU) and metformin therapy.

Methods: This was a retrospective cohort study using the 2006–2010 national health insurance claims database from the Health Insurance Review ? Assessment Service (HIRA), Korea. Patients aged 20–99 years with type 2 diabetes taking DPP-4 inhibitor and metformin therapy or SU and metformin therapy were included between December 1, 2008 and December 31, 2009, with no history of study drug prescription in previous 1 year. Incident CV events of ischemic heart disease, heart failure, ischemic stroke, transient ischemic attack, atherosclerosis, aortic aneurysm requiring hospitalization or emergency department visit or coronary revascularization procedure were identified. Rate ratio and 95% confidence intervals (95% CI) for CV disease risk associated with use of DPP-4 inhibitor and metformin therapy relative to SU and metformin therapy was estimated from Cox proportional hazards model.

Results: We identified 235,616 initiators of SU and metformin therapy and 151,866 initiators of DPP-4 inhibitor and metformin therapy. Compared to those treated with SU and metformin therapy, the adjusted rate ratio of CV disease was 0.92 (95% CI, 0.87–0.98) for DPP-4 inhibitor and metformin therapy.

Conclusions: DPP-4 inhibitor and metformin therapy is associated with a significantly lower risk of CV disease than is SU and metformin therapy.

506. GLP-1 Agonists (Exenatide and Liraglutide) and the Risk of Cancer: A Meta-Analysis of Published Randomized Controlled Clinical Trials

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Background: The potential association between exenatide (Byetta), a GLP-1 agonist, and cancer development, in particular pancreatic cancer and thyroid neoplasms, has been discussed. The European Medicines Agency (EMA) assessment of exenatide' benefit-risk ratio remained positive, with the recommendation of an additional epidemiologic study. Besides exenatide, another GLP-1 agonist, liraglutide (Victoza), holds an EU marketing authorisation, since 2009.

Objectives: This study was aimed at evaluating the risk of developing cancer in patients treated with exenatide or liraglutide, according to the data published in the randomized clinical trials (RCT).

Methods: A meta-analysis was carried out pooling data from studies identified on a Medline and on a Cochrane Library search. Public available records from EMA were also searched. Studies were included if they were RCTs, evaluating exenatide or liraglutide in type 2 diabetes mellitus, using active or placebo as control. Relative risks

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(RR) were estimated using random-effects models and statistical heterogeneity was estimated with I^2 statistics.

Results: Of the 218 retrieved publications, 14 RCTs met the inclusion criteria. Of those, six evaluated exenatide and nine evaluated liraglutide. One RCT directly compared exenatide and liraglutide. Twenty-four neoplasms were identified in the exenatide RCTs, 15 of which in exenatide-treated patients. RR for exenatide exposure and cancer was 0.96, 95% CI 0.33–2.80, $I^2 = 14\%$. Of the 51 neoplasms identified in nine liraglutide RCT's, 39 were found in liraglutide-treated patients. The risk for cancer occurrence due to liraglutide exposure was RR 1.46, 95% CI 0.76–2.83, $I^2 = 0\%$.

Conclusions: The results don't provide evidence for an increased risk of cancer occurred during the treatment with GLP-1 agonists. However, the safety profile of both exenatide and liraglutide deserves to be closely monitored since the length of exposure during their clinical development may not be long enough to perform a correct assessment.

507. Acute Pancreatitis Associated with GLP-1 Agonists (Exenatide and Liraglutide) Exposure: A Meta-Analysis of Published Evidence

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Background: Post-marketing surveillance – spontaneous reports - of exenatide (Byetta), a GLP-1 agonist approved for type 2 diabetes mellitus, raised the possibility for its association with acute pancreatitis (AP). On request of the FDA, an update of the exenatide' product labelling was carried out. Latter, in 2009, another new GLP-1 agonist, liraglutide (Victoza), was approved by the European Medicines Agency (EMA).

Objectives: This study was aimed at identifying the risk of developing AP in patients exposed to exenatide or liraglutide, according to the published evidence from both experimental and observational studies.

Methods: A meta-analysis was carried out pooling data from studies identified on a Medline and on a Cochrane Library search. Public available records from EMA were also searched. Studies were included if they evaluated exenatide or liraglutide in type 2 diabetes mellitus, using active or placebo as control. Relative risks (RR) were estimated using random-effects models and statistical heterogeneity was estimated with I^2 statistics.

Results: Of the 218 retrieved publications, eight studies met our inclusion criteria. For exenatide, two retrospective cohort studies and three randomized controlled trials (RCTs) were included. RR for exenatide exposure and AP was 0.67, 95% CI 0.42–1.07, $I^2 = 15\%$. Subgroup analysis of observational or experimental studies yielded a similar RR. Three RCTs evaluating liraglutide on type 2 DM reported data on AP. The RR for AP occurrence due to liraglutide exposure was 1.30, 95% CI 0.24–7.21, $I^2 = 0\%$.

Conclusions: These findings don't provide evidence for an increased risk of AP during the treatment with GLP-1 agonists. However, further experimental and observational studies are needed to confirm such findings due to the limitations of currently available data: number of patients exposed to the treatments and length of exposure.

508. Active Monitoring of the Comparative Effectiveness and Safety of Prasugrel vs. Clopidogrel in Routine Care

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Background: Prasugrel is an antiplatelet agent approved for marketing in the US in 2009. In the Phase 3 trial that supported its approval, prasugrel, as compared to clopidogrel, reduced cardiovascular event rates but increased bleeding risk. It is not known how the effectiveness and safety of these agents compare in clinical practice.

Objectives: To perform sequential monitoring comparing ischemic and bleeding outcomes among patients initiating prasugrel vs. clopidogrel in routine care.

Methods: Using the HealthCore Integrated Research Database, we defined the first monitoring period as the 6 months following prasugrel introduction and refreshed the data on a bimonthly basis to form subsequent monitoring periods. Within each period, we identified patients discharged from hospitalizations for acute myocardial infarction (AMI) or acute coronary syndrome who initiated prasugrel or clopidogrel with no use of either drug in the prior year. We 1:1 matched patients using high-dimensional propensity scores (hd-PSs) that we calculated separately in each period. We followed patients over the duration of their index treatment to ascertain ischemic (AMI) and bleed (hemorrhagic stroke, gastrointestinal [GI] bleed) events. For each outcome, we selected and applied sequential alerting algorithms from a statistical simulation study.

Results: We identified 939 eligible new users of prasugrel and 7,060 eligible new users of clopidogrel over the first 21 months of prasugrel availability in the US. In the hd-PS matched sequential cohorts, the AMI rate difference

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(RD) comparing prasugrel to clopidogrel was -11.6 (95% CI, -60.7, 37.6) events per 1,000 person-years and RDs were -2.6 (-20.1, 15.0) and -3.8 (-11.1, 3.6) for GI bleed and hemorrhagic stroke, respectively. No algorithms generated alerts for any of the outcomes.

Conclusions: Our results provide support for the feasibility of a prospective monitoring system for new drugs. No substantial differences in outcome event rates have been observed and no alerts have been generated suggesting that, as used in practice, prasugrel relative to clopidogrel is not associated with major concerns related to the outcomes that we evaluated.

509. The Effect of the Timing of Oral Hormonal Emergency Contraceptives on Pregnancy Rate

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Background: Women who wish to take oral hormonal emergency contraceptives (ECs) have a limited window of time within which the medications can be effective. In many publications, this window has been defined as 72 or 120 hours after the act of unprotected intercourse.

Objectives: To evaluate the effect of the timing of ECs on the pregnancy rate with adjustment for differences in covariates.

Methods: This research is part of a comparative effectiveness study of EC regimens. The cohort comprised women who received ECs within a 25-month period. Administrative data collected at the time of EC dispensing were used to estimate the timing of EC after the index intercourse, the day of the index intercourse in the menstrual cycle, and the expected pregnancy rate. Linked health data were used to identify pregnancy-related health services within 42 weeks after EC dispensation. Three physician experts adjudicated the compatibility of pregnancy-related events with the index act of intercourse. Pregnancy rate was stratified by categories of time between the index intercourse and EC dispensing. The effect of time on the odds of pregnancy was analyzed with logistic regression, adjusting for potential confounders.

Results: Data from 7,493 women were analyzed. The baseline expected pregnancy rate in the absence of EC was approximately 4.1% in all time categories. The pregnancy rates of women who received ECs at 0–12, 13–24, 25–36, 37–48, 49–60, 61–72, and >72 hours were 2.1%, 2.3%, 2.5%, 2.9%, 3.0%, 3.8%, and 3.7%, respectively. The odds ratio for pregnancy increased with time, relative to the first category (0–12 hours). The trend observed without adjustment was similar to that obtained after adjusting for age, EC regimen type, and the menstrual cycle day on which the index intercourse occurred.

Conclusions: The effect of ECs declined with time and appeared to be very limited beyond the first 60 hours after intercourse in a cohort of women treated under routine clinical conditions.

510. Comparative Efficacy of Intermittent vs. Continuous Androgen Deprivation Therapy in Advanced Prostate Cancer: A Meta-Analysis

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Background: Androgen deprivation therapy (ADT) is widely used as treatment for advanced prostate cancer. ADT can be administered continuously or intermittently based on changes of prostate-specific antigen levels. Compared with continuous ADT, intermittent ADT is anticipated to offer several advantages, such as delayed progression to hormone-refractory disease, improved quality of life as well as reduced medical cost for ADT. However, it is unclear whether intermittent ADT provides comparable clinical efficacy (survival) to continuous ADT.

Objectives: To summarize available evidence from randomized controlled trials that compared the efficacy of intermittent vs. continuous ADT in advanced prostate cancer.

Methods: We conducted a systematic search of several bibliographic systems (PubMed, EMBASE, and Web of Science databases) to identify all randomized trials of intermittent and continuous ADT in advanced prostate cancer. Data extraction included information of mortality outcomes (any-cause mortality and cancer-specific mortality), trial designs, and participants demographics. We calculated the summarized relative risk and 95% confidence intervals (CIs) using fixed- and random-effects models.

Results: We identified seven trials assessing mortality outcomes after IADT vs. CADT, including a total of 4,781 men with advanced prostate cancer. Men receiving IADT showed similar risk of any-cause mortality (risk difference, RD) = 0.01, 95% CI = -0.03, 0.04; risk ratio, RR = 0.99, 95% CI = 0.93, 1.06) and disease-specific mortality (RD = 0.02, 95% C.I. = 0.00, 0.05; RR = 1.06, 95% C.I. = 0.93, 1.21), compared to men receiving CADT.

Conclusions: IADT for treatment of men with newly diagnosed and recurrent advanced prostate cancer appears to

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have comparable efficacy as CADT in reducing risk of any-cause mortality and prostate cancer mortality. Further research on other risks or benefits of IADT, such as changes in the risk of diabetes and cardiac dysfunction, and impacts on quality of life, is needed to fully inform treatment decisions.

511. Comparative Safety and Effectiveness of Generic vs. Branded Alendronate in Medicare Population

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Background: Generic medications may provide broader access to treatment for seniors. However, it remains unclear whether the generic and branded alendronate products are equivalent in terms of safety and effectiveness.

Objectives: We evaluated fracture incidence rates and upper gastrointestinal bleeding among Medicare beneficiaries initiating branded vs. generic alendronate during 2007–2009.

Methods: Using the Medicare national random 5% sample, we identified new users of generic alendronate, branded alendronate without D and branded alendronate with D. Eligible subjects were ≥65 years of age; continuously enrolled in Medicare parts A, B and D and not in a Medicare Advantage plan; and newly treated during 2007–2009 (no prior use of any prescriptions of osteoporosis medications in last 12 months). Exposures defined by prescription covered person days and up to 90 days without subsequent refill. Cox proportional hazards models evaluated associations between different alendronates and hip fracture, clinical vertebral fracture and hospitalized upper gastrointestinal bleeding.

Results: The study included 7,980 new users of brand alendronate without D, 2,339 of brand alendronate with D, and 17,889 of generic alendronate. During follow-up, 296 subjects had hip fractures, 353 had clinical vertebral fractures and 116 had upper gastrointestinal events. After multivariable adjustment and compared to brand alendronate without D, hazard ratios were: (1) for hip fractures, 0.87 (95% confidence interval (CI): 0.58–1.31) for brand alendronate with D and 0.81 (95% CI: 0.63–1.06) for generic alendronate; (2) for clinical vertebral fracture, 1.04 (95% CI: 0.73–1.48) for brand alendronate with D and 0.89 (95% CI: 0.70–1.14) for generic alendronate; 3) for upper GI bleeding, 0.74 (95% CI: 0.37–1.45) for brand alendronate with D, and 0.85 (95% CI: 0.56–1.29) for generic alendronate.

Conclusions: Compared brand alendronate, generic alendronate appeared to have comparable effectiveness for fracture and safety in a large cohort of new users enrolled in Medicare.

512. Comparative Safety of Conventional and Atypical Antipsychotics and the Risk of Ischemic Stroke among the Elderly

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Background: Controversial concern has been raised up about whether the risk of ischemic stroke differs between conventional antipsychotics (CAP) and atypical antipsychotics (AAP).

Objectives: This study is performed to compare the risk of hospitalization for ischemic stroke between CAP and AAP among elderly patients.

Methods: We conducted retrospective cohort study using the Korea Health Insurance Review ? Assessment Service database. A cohort consisted of an elderly patients who newly prescribed antipsychotics between January, 1, 2006 and December, 31, 2009. Drug exposures were categorized as following: haloperidol (HAL), chlorpromazine (CHL) as CAP and risperidone (RIS), quetiapine (QUE), olanzapine (OLA) as AAP. Patients with prior cerebrovascular diseases (ICD-10, I60-I69), TIA (ICD-10, G45) during prior 365 days were excluded. Study subjects were observed until first hospitalization to the ischemic stroke (ICD-10, I63). Multivariable Cox regression models were used to estimate the hazard ratio (HR) and 95% confidence intervals (95% CI). Standardized mobility ratio (SMR) were used to control for potential confounding.

Results: Among total 71,584 patients, 24,668 patients on RIS, 15,860 patients on QUE, 3,888 patients on OLA, 19,564 patients on HAL, 7,604 patients on CHL were identified. Incidence rate was higher for those on CHL (7.99), HAL (6.09) in the CAP compared to the QUE (4.16), OLA (2.79), RIS (3.01) in the AAP per 1,000 person-year. Substantially increased risk was observed among CHL (HR = 3.47, 95% CI, 1.97-5.38), followed by HAL (HR = 2.43, 95% CI, 1.18–3.14), QUE (HR = 1.23, 95% CI, 0.78–2.12) and OLA (HR = 1.12, 95% CI, 0.59–2.75).

Conclusions: A very strong risk of ischemic stroke was observed in the CAP users. The evidence showed that CAP should not be prescribed in the elderly, prescribing AAP is highly recommended.

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513. Changes after Reformulation of Extended-Release Oxycodone in Calls to US Poison Centers for Oxycodone and Heroin

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Background: Extended-release (ER) oxycodone was reformulated so that tablets are more difficult to crush and form a gel when dissolved, but the effects on abuse are not known. In August 2010, Purdue stopped shipping original ER oxycodone (OC) and started shipping reformulated ER oxycodone (ORF).

Objectives: To assess changes in the number of calls to poison centers reporting problems from exposure to ER oxycodone ("exposures"), other single-entity (SE) oxycodone and heroin from before to after ORF introduction.

Methods: The American Association of Poison Control Centers maintains a database of calls to all 61 US poison centers reporting problems due to drug exposures. These are a proxy measure for serious adverse events from a drug. Exposures are classified by reason (e.g., intentional abuse, unintentional therapeutic errors). Changes in numbers of exposures were assessed from before (July 2009 to June 2010) to after (October 2010 to June 2011) ORF introduction. To differentiate between ORF effects and secular trends, trends one year earlier (July 2008 to June 2010) were assessed.

Results: Exposures for all reasons decreased by 19% for ER oxycodone (693–568 cases per quarter), increased 13% for other SE oxycodone (1509–1705 per quarter) and increased 17% (587–688 per quarter) for heroin from before to after reformulation. Exposures resulting from abuse decreased by 25% for ER oxycodone, increased by 17% for other SE oxycodone and increased by 21% for heroin from before to after reformulation. Unintentional therapeutic error exposures among patients decreased 13% for ER oxycodone and increased 10% for other SE oxycodone from before to after reformulation. One year earlier (July 2008 to June 2009 vs. October 2009 to June 2010), exposures for all reasons increased 8% for ER oxycodone, increased 11% for other SE oxycodone and increased 5% for heroin.

Conclusions: Poison centers exposures for any reasons to Purdue's ER oxycodone decreased after reformulation, as did exposures for the reasons of abuse and patient therapeutic error, while in the same period exposures to other SE oxycodone and heroin increased. Longer follow up is needed and is ongoing.

514. Impact of Long-Acting Injectable vs. Oral Antipsychotics on Rehospitalization Rates and Emergency Room Visits among Relapsed Schizophrenia Patients

Marie-Hélène Lafeuille,[1] François Laliberté-Auger,[1] Patrick Lefebvre,[1] Christian Frois,[2] John Fastenau,[3] Mei Sheng Duh.[2] *[1]Groupe d'analyse, Ltée, Montréal, QC, Canada; [2]Analysis Group, Inc., Boston, MA, United States; [3]Janssen Scientific Affairs, LLC, Titusville, NJ, United States.*

Background: Long-term pharmacological therapy for patients with schizophrenia is directed at the prevention of relapse, often leading to re-hospitalization.

Objectives: To compare the impact of switching to long-acting atypical antipsychotic therapy (LAT) vs. continuing with oral antipsychotics (APs) on the recurrence of hospitalizations and emergency room (ER) visits among schizophrenia patients who relapsed.

Methods: Hospital discharge and billing records from the Premier Perspective™ Comparative Hospital Database (2006Q1–2010Q4) were analyzed. Adult patients receiving oral APs during a schizophrenia-related hospitalization were identified and further stratified upon their next schizophrenia-related rehospitalization (i.e., relapse) into the following exposure groups: (1) patients switching to LAT vs. (2) patients continuing with oral APs. LAT relapse patients were matched 1:3 with oral AP relapse patients using a propensity score model. The Andersen-Gill extension of the Cox proportional hazards model was used to assess the impact of LAT vs. oral AP on time to multiple recurrences of hospitalizations and ER visits.

Results: A total of 1064 LAT patients were matched with 3015 oral AP patients and formed the study population. LAT and oral AP groups were well-balanced with respect to age, gender, race, region, payer, hospital characteristics, admitting diagnoses, and degree of illness severity ($p > 0.05$ for all). Over a mean 30-month follow-up period, LAT patients were associated with significantly lower rates of all-cause rehospitalizations (1.27 vs 1.61, $p < 0.0001$) and ER visits (2.36 vs 2.68, $p = 0.0195$) compared with oral AP patients. Based on Andersen-Gill models, all-cause rehospitalization rates (hazard ratio [HR] = 0.82, 95% CI: 0.77–0.87, $p < 0.0001$) and ER visits (HR = 0.89, 95% CI: 0.87–0.94, $p < 0.0001$) were significantly lower for LAT than for oral AP. Consistently significant results were found when restricting to mental disorder–related events.

Conclusions: This hospital database analysis found that in relapsing schizophrenia patients, LATs were associated with lower rehospitalization and ER-visit rates.

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515. The Impact of Long-Acting Injectable vs Oral Antipsychotics on Hospitalization Rates in Patients with Schizophrenia: A Systematic Review and Meta-Analysis

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Background: Long-term pharmacological therapy for patients with schizophrenia is directed at the prevention of relapse, often leading to re-hospitalization.

Objectives: To compare, by performing a meta-analysis, the impact of long-acting injectable antipsychotics (LAIs) vs. oral atypical antipsychotics (OAs) on hospitalizations among schizophrenia patients.

Methods: Using the PubMed database and major psychiatric conference proceedings, a systematic literature review for 01/2000–06/2011 was performed to identify studies evaluating schizophrenia patients treated with antipsychotics. Studies reporting hospitalization rates as a percentage of patients hospitalized or as the number of hospitalizations per person per year were selected. The primary endpoint for the meta-analysis was percentage decrease in hospitalization rates from baseline during treatment. Pooled treatment-effect estimates were calculated using random-effect models. Meta-regressions adjusted for study-level characteristics to account for the heterogeneity across studies. A sensitivity meta-regression analysis estimating the treatment effect on absolute hospitalization rates was also conducted.

Results: Fifty-three studies evaluating 81 treatment arms (LAIs = 15 arms, 5294 patients; OAs = 66 arms, 96,013 patients) were identified. Reduction in hospitalization rates for LAIs was 24.5 percentage points higher than for OAs (random-effect estimates: LAIs = 60.0% vs. OAs = 35.5%, p = 0.018). Based on a meta-regression analysis, controlling for age, sex, refractory schizophrenia, and study characteristics, the adjusted percentage reduction in hospitalization rates for LAIs was 36.9 percentage points (LAIs = 66.4% vs. OAs = 29.5%, p = 0.024) higher than for OAs. The sensitivity analysis based on absolute hospitalization rates corroborated these findings (adjusted hospitalization rate during follow-up was 12.6% lower for LAIs than for OAs; LAIs = 13.7% vs. OAs = 26.2%, p = 0.033).

Conclusions: Results of this meta-analysis suggest that LAIs significantly reduce hospitalization rates for schizophrenia patients compared to OAs.

516. Switching the Pharmaceutical Dosage Form of Extended-Release Valproate Is Associated with Therapeutic Modification of Antiepileptic Therapy

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Background: Product switching of extended release (ER) antiepileptic drugs (AED) is discussed controversially since evidence from bioequivalence studies may not translate into clinical practice.

Objectives: To explore whether two different aspects of product switching – a change of pharmaceutical manufacturer or a change of the pharmaceutical dosage form – in patients treated with ER valproic acid/valproate (VPA) is associated with therapeutic modification of AED therapy, i.e., prescribing of an additional AED as a proxy for treatment failure.

Methods: A cohort study was performed utilizing the DAPI database of ambulatory drug claims from more than 80% of German community pharmacies. Patients initiating VPA therapy with ER dosage forms between 2003 and 2006 and filling a second prescription (index) within 180 days were included. Time periods between subsequent VPA prescriptions were classified as product switch if a different ER VPA product was dispensed, considering information on a different manufacturer as well as the type of pharmaceutical dosage form (monolithic vs. multi-unit). Patients were followed from the index date until the occurrence of the event (prescription of additional AED) or censoring (due to interruption or discontinuation of ER VPA treatment, or 12/31/2009, the latest). Hazard ratios (HR) for the event were estimated using proportional hazards regression modelling with time-varying exposure.

Results: Of 78,427 medication profiles were identified of which 15,065 (19.2%) experienced the event. Switching the type of the dosage form was associated with an increased hazard for the event compared to no switch (switch from monolithic to multi-unit dosage forms: HR = 1.43 [99% CI 1.16–1.77]; switch from multi-unit to monolithic: HR = 1.36 [1.10–1.67]), whereas switching between different pharmaceutical manufacturers was not (HR = 1.01 [0.92–1.12]).

Conclusions: Switching of ER VPA products is associated with an increased risk of AED regimen modification, and the type of pharmaceutical dosage form is probably more influential than differences between pharmaceutical manufacturers.

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517. Pharmacotherapy Is More Effective in Childhood Than in Juvenile Absence Epilepsy in Long-Term Follow-Up

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Background: There is a strong opinion about therapeutic efficacy of valproic acid preparations in all forms of idiopathic generalized epilepsy (IGE). Efficacy of pharmacotherapy is traditionally evaluated after 6 months or 1 year of treatment. However, there is uncertainity about the long-term efficacy of pharmacotherapy in patients with IGE.

Objectives: To compare effectiveness of pharmacotherapy of Childhood vs. Juvenile absence epilepsy.

Methods: Patients with Childhood (eight boys and 12 girls, mean age – 11 ± 0.4 years) and Juvenile (three boys and nine girls, mean age – 16 ± 0.7 years) absence epilepsy (CAE and JAE) were followed for 10 years in outpatient epilepsy clinic in 2001–2011. We calculated Risk Ratio (RR with Review Manager 5.2) using remission lasting for 3 years or longer as an outcome measure.

Results: Monotherapy was used in 17/20 (85%) of CAE cases – all with valproic acid (mean daily dose – 29 ± 1 mg/kg/day); polytherapy (valproic acid + succinamide, valproic acid + lamotrigine) was used in 3/20 (15%) of cases. Monotherapy was used in 9/12 (75%) of JAE cases: with valproic acid in 8/9 (89%) of monotherapy cases (mean daily dose – 25 ± 2 mg/kg/day) and lamotrigine in 1/9 (11%). Polytherapy (valproic acid + succinamide) was used in 3/12 (25%) of all JAE cases. Remission lasting for more than 6 months was observed in 17/20 (85%) of patients with CAE and 11/12(92%) of patients with JAE. Remission lasting longer than 1 year was achieved in 17/20 (85%) of patients with CAE and in 9/12 (75%) of patients with JAE. Remission lasting longer than 3 years was achieved in 13/20 (65%) of patients with CAE and 2/12 (17%) of patients with JAE. RR for remission lasting longer than 3 years for CAE vs. JAE was 3.90; 95%CI [1.06–14.39], $p < 0.05$.

Conclusions: Long-term follow up shows higher treatment response rate in patients with childhood vs. juvenile absence epilepsy.

518. Does Long-Acting Injectable Risperidone Make a Difference to the Real-Life Treatment of Schizophrenia? Results of the French Cohort for the General Study of Schizophrenia (CGS)

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Background: Treatment non-adherence is a major cause of recurrence in schizophrenia. Delayed release formulations like risperidone long-acting injectable (R-LAI) may reduce rehospitalisation.

Objectives: The primary aim of this study was to compare the impact of R-LAI to other antipsychotics on the rates of hospitalisation in real-life settings.

Methods: The French Cohort for the General study of Schizophrenia (CGS) recruited 2092 DSM-IV diagnosed schizophrenia patients from 177 psychiatric wards of public and private hospitals across France. These patients were ambulatory or had been hospitalised for < 93 days at study entry. Patients were followed for one year during which to antipsychotic use and frequency of hospitalisation was assessed. Recruitment was stratified for long-acting second generation antipsychotic use. A multivariate Poisson regression adjusted for confounding with propensity scores and allowing for autocorrelation was used for the calculation of adjusted relative rates of hospitalisation with 95% confidence intervals.

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Results: A total of 1,859 out of 2,092 eligible patients were included in the analysis. The mean age was 37.65 years, 68.3% were male and 36.7% were hospitalised for <93 days at study entry. Altogether, 1,,859 patients (89.2%) were followed up over 12 months accumulating 796 hospital stays (53.4 per 100 person-years). R-LAI patients were younger and had been hospitalised more often in the past 12 months compared to non-R_LAI users. In an adjusted Poisson Regression analysis R-LAI use was associated with a lower rate of hospitalisation 0.66 [0.46–0.96] compared to non-R-LAI use and 0.53 [0.32–0.88] compared to use of other LAI's.

Conclusions: Use of R-LAI was associated with lower rates of hospitalisation compared to non-use of R-LAI.

519. Tacrolimus vs. Cyclosporine in Maintenance Immunosuppressive Regimens in Renal Transplantation in Brazil (2000/2004), a Cost-Effectiveness Matched Analysis

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Background: In Brazil, the National Health System (SUS) is responsible for almost all renal transplants. SUS protocols recommend using cyclosporine, in association with azathioprine and corticosteroids, to maintain the immunosuppression essential for successful renal transplant. Alternatively, cyclosporine (CsA) can be replaced by tacrolimus (Tac).

Objectives: The aim of this study was to evaluate for the perspective of SUS the cost-effectiveness of therapeutic schema involving cyclosporine or tacrolimus after renal transplant during a 60 month follow-up period.

Methods: A record linkage of national health databases with data from hospital, ambulatory, specialized medicines and mortality has been carried out and a historical cohort from 2000 to 2004 was established with patients who underwent renal transplant and received cyclosporine or tacrolimus matched 1:1. Multivariate analyses were performed using the Cox model to examine factors associated with progression to treatment failure. Kaplan-Meier method has been used to evaluate patient and graft survival and at last was performed a cost-effectiveness analysis from SUS perspective.

Results: Among 9,298 renal transplants with living donors and deceased were identified 8,981 different patients. Of these it was observed that 49% of patients using only immunosuppressive regimens based on cyclosporine and 14% on totacrolimus. After pairing in 1:1 between tacrolimus and cyclosporin groups by the variables: type of transplant, sex, age and year of transplant was possible to make 1,011 pairs. Most of the patients were female, age 36.7 years, for whom the most frequent primary diagnosis of chronic renal failure (CRF) were glomerulonephritis/nephritis. Cost-effectiveness evaluation pointed for dominance of CsA over Tac as total cost per patient to 1st year and for 5 years of treatment are lower with a higher amout of life years gained.

Conclusions: After matching 1:1 patients of CsA and Tac wasn't evidenced advantage of better effectiveness for patients using Tac regimens. Economic evaluation has shown that CsA regimens were more cost-effective (dominance) over Tac.

520. Dose-Response Relationship between Post-Progression Bevacizumab Exposure and Survival among Metastatic Colorectal Cancer Patients

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Background: At the 27th ICPE, we presented the results of two large observational cohort studies that examined the effect of bevacizumab (BV) treatment beyond disease progression (PD) on post-progression survival among metastatic colorectal cancer (mCRC) patients: BRiTE (conducted 2004–2008) and ARIES (2006–2012). In these analyses, post-progression BV treatment was treated as a time-fixed, dichotomous exposure. The current analysis applies a time-dependent approach to capture the dynamic variations in post-progression BV treatment, including duration and intermittency, observed in the real world and mitigates several of the limitations of the earlier analyses.

Objectives: To describe a cumulative exposure analytical approach to estimate BV treatment effect beyond PD in the ARIES observational cohort study.

Methods: ARIES enrolled 1,550 mCRC pts receiving 1st line chemotherapy plus BV from 248 sites in 43 states. Data were collected via electronic data capture prospectively at baseline and quarterly. PD was determined by the investigator via clinical and/or radiographic assessment. Each BV administration was collected. The dose–response relationship between cumulative BV treatment and post-progression survival was evaluated using a multivariable time-dependent Cox proportional hazard model. BV exposure was defined as the cumulative doses of BV after first PD through the end of follow-up. This model was chosen in order to minimize survival bias in favor of those living longer.

Results: As of the February 14, 2011 data cutoff, 1,183 (76%) patients had experienced and survived a first PD. The hazard ratios for post-progression survival decreased, on average, by 2.1% (range, 1.7%–2.5%) with each additional BV dose across follow-up. Cumulative BV exposure

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was associated with improved post-progression survival ($p < 0.0001$).

Conclusions: This analysis suggests that cumulative exposure to BV after PD is associated with corresponding increases in post-progression survival among mCRC patients. This analysis also serves as a proof-of-concept for assessing treatment effect in the real-world setting capturing the variations in real-world treatment patterns.

521. Imunossupressive Therapy Impact in Kidney Transplant

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Background: To prevent graft rejection different immunosuppressive therapy protocols are used in kidney transplant.

Objectives: Evaluate the impact of immunosuppressive therapy in graft survival rate.

Methods: A retrospective cohort study was performed including 286 patients that have been transplanted between 1995 and 2007 in a transplant center in Portugal. Graft loss was defined as return to dialysis or death related with the transplant. In the study period, patients were exposed to three different immunosuppressive protocols: cyclosporine + micophenolate mofetil + prednisolone (1); tacrolimus + micophenolate mofetil + prednisolone (2); conversion of 1–2 (3); sirolimus + prednisolone (4). Recipients were grouped according to type of immunosuppressive protocol, thus generating several cohorts. Kaplan–Meier estimates and Cox regression were used to estimate graft survival for each cohort.

Data were collected from the clinical registries.

Results: Most patients were male (68.3%) with a mean age of 49 years at the time of transplant. Total time of follow-up was 130 months (10.8 years). The majority of patients were exposed to protocol 1 (59.8%), followed by protocol 2 (15.4%). Forty one patients were converted from protocol 1 to protocol 2 and 30 (10.5%) were exposed to protocol 4. Global survival was respectively: 1 year 88.4%; 3 years 82.1%; 5 years 75.0% and 10 years 46.2%, with a median of global time of 115.17 months (9.59 years) (IC 95%: 99.94–130.40). One year after transplant the survival related to protocol 1 was 83.0% and for protocols 2 and 4 was 100%. In relation to protocol 1: patients that were exposed to protocol 2 had a risk reduction of 10.4% (HR = 0.896; IC 95%: 0.376–2.137) ($p = 0.805$). Patients that were converted from protocol 1 to protocol 2 had a risk reduction of 56.7% (HR = 0.433; IC 95%: 0.208–0.898) ($p = 0.025$) and patients in protocol 4 a risk reduction of 56.9% (HR = 0.431; IC 95%: 0.199–0.934) ($p = 0.033$).

Conclusions: Graft global survival was similar to that reported in other transplant centers. The introduction of new immunosuppressive therapy, namely tacrolimus and sirolimus has enlarged the limited therapeutic options, which increase the survival of patients undergoing renal transplantation.

522. Impact of Oropharyngeal Exercises on Patients with Moderate Obstructive Sleep Apnea

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Background: Upper airway function plays role in the maintenance of the upper airway patency and contributes to the genesis of the obstructive sleep apnea (OSA). A narrowed upper airway is very common among OSA patients, and is usually in adults. The vibration or collapse of the soft palate is a significant contributor to snoring of OSA.

Objectives: The study was aimed to find the impact of oropharyngeal exercise on patients with moderate obstructive sleep apnea.

Methods: A total of 34 patients with (Apnea Hypopnea Index (AHI) 15–29.9) were included. Prior to the onset of oropharyngeal therapy and polysomnography, each patient completed a validated Epworth sleepiness scale (ESS) and Quebec sleep questionnaire (QSQ) and baseline measurements are recorded. Patients were given oropharyngeal exercises and asked to perform the exercises regularly about 30 minutes for 3 months. After 3 months the QSQ and ESS was readministered. The study was conducted at private corporate hospital to study the severity of OSAS and neck circumference, snoring time, Number of Snoring, Oxygen desaturation, Daytime sleepiness and quality of life.Pearson correlation and paired "t" test were applied.

Results: Out of 34 patients 29 were male and five were female. The mean Age and body mass index (BMI) of total study population were 50.18 ± 10.75 and 28.53 ± 4.03. While comparing the polysomnographic variables there was a significant difference between baseline and after therapy ($p < 0.05$). ESS at baseline 12.12 ± 3.47 after therapy 8.74 ± 2.08 ($p < 0.0001$), neck circumference at baseline 39.27 ± 0.87 after therapy 38.32 ± 2.06 ($p < 0.0256$). There was a significant changes were observed in all domains of QSQ ($p < 0.05$). Significant Correlation was observed for AHI with neck circumference ($p < 0.00036$), and BMI ($p < 0.0467$).

Conclusions: Among the study population there was a significant improvement in the severity of disease, quality of life, day time sleepiness and neck circumference. Our results also suggest that oropharyngeal exercises has sig-

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nificant impact on patients with moderate obstructive sleep apnea.

523. Management of Patients with Colon Cancer in France: Description of the Cohort FDRK (Feuille De Route Cancer du Côlon (K))

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Background: The course of patients with colorectal cancer in France is little studied. Improving its knowledge is essential in order to guide the structuring of care provision and care of patients.

Objectives: The cohort FDRK is a national prospective observational study conducted to describe the care pathway of patients with colon cancer, according to the characteristics of patients and their tumors.

Methods: Among the centers that care colon cancer in France, a random sample taking into account the size and type of canter has been identified. Inclusion criteria for patients were: age > 18 years, adenocarcinoma of the colon or rectum with histological diagnosis ≤3 months (patient incidents) or > 3 months metastases diagnosis in the first 3 months (prevalent patients). Data on patient demographics, clinical features, characteristics of cancer and the patient's care were collected prospectively at baseline, at 6 months (± 2 months) and 12 months (± 2 months).

Results: Between June 2006 and April 2008, 1188 incident patients (median age 67 years, sex ratio M/F = 1.3) and 76 prevalent patients (median age: 67.5, sex ratio M/F = 1.3) were included by 97 centers throughout France. Participating services were gastroenterology (38%), surgery (33%), oncology (26%) and general medicine (3%). Among incident cases, 841 (71%) had no metastases at baseline and 347 (29%) had synchronous metastases. Thirteen per cent of cases were diagnosed during an endoscopy or surveillance. AJCC stage distribution of incident cases was: 2% carcinoma in situ, stage I:9%, stage II:28%, stage III:31% and stage IV:30%. Eighty-four per cent of patients underwent a multidisciplinary meeting. The median follow-up was 13 months. Patients lost to follow-up were 0.85 and 7.75 at 6 and 12 months respectively. One hundred seventy-three patients died during follow-up.

Conclusions: FDRK is the first French cohort of patients with colon cancer representing current practices at the national level. It gets to know the care of patients regardless of the type of institution, the patient profile and the stage of the disease. FDRK can afford to contribute to decision making in public health, enabling better management of colorectal cancer.

524. Abstract withdrawn by author.

525. Comparative Safety of Inhaled Medications in Patients with Chronic Obstructive Pulmonary Disease: Systematic Review and Mixed Treatment Comparison Meta-Analysis of Randomized Controlled Trials

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Background: The active-treatment comparative safety information across a variety of inhaled medications in patients with chronic obstructive pulmonary disease (COPD) is limited.

Objectives: To comprehensively examine and compare the risk of overall and cardiovascular death for inhaled medications in patients with COPD.

Methods: We searched the databases of MEDLINE, CINAHL, Cochrane Library and ClinicalTrial.gov from inception to July, 2011 to identify randomized controlled trials of tiotropium Soft Mist™ Inhaler, tiotropium HandiHaler®, long-acting beta-2 agonists (LABA), inhaled glucocorticosteroids (ICS), and LABA-ICS combination with 6-month study durations or more. Two investigators independently applied selection criteria, evaluated identified trials, and retrieved relevant characteristics from eligible trials. The direct comparison and mixed treatment comparison (MTC) meta-analyses were conducted to estimate the pooled odds ratios of death for each treatment comparison.

Results: Forty-two eligible trials with 52,516 individuals were included in the analysis. The MTC meta-analysis based on the fixed effect model indicated tiotropium Soft Mist™ Inhaler was associated with an universally increased risk of overall death as being compared with placebo (OR: 1.51; 95% CI: 1.06, 2.19), tiotropium HandiHaler® (OR: 1.65; 95% CI: 1.13, 2.43), LABA (OR: 1.63; 95% CI: 1.10, 2.44), and LABA-ICS (OR: 1.90;

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95% CI: 1.28, 2.86). The risk was more pronounced for cardiovascular death, in patients with severe COPD, and at a higher daily dose. On the contrary, LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium HandiHaler® or LABA. Results of MTC were similar to those of the direct comparison meta-analysis, with less precision in the random effects model.

Conclusions: Our study described a comparative safety profile for each category of inhaled medications. Tiotropium Soft Mist™ Inhaler was with a significant risk of death and should be used with caution.

526. Challenges of IPTW Estimation with Combined Exposures: An Example Using Hemodialysis Data

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Background: Most hemodialysis patients are treated with intravenous iron and erythropoiesis-stimulating agents, which likely have interactive effects on iron parameters and clinical outcomes. Propensity scoring with inverse probability of treatment weights (IPTW), common in comparative effectiveness research, is complicated by combined exposures.

Objectives: With the eventual goal of assessing the effects of different iron dose levels, we compared IPTW approaches with regard to the distribution of weights and the resulting covariate balance.

Methods: With 2006–2008 hemodialysis patient data (N = 4,893) from a small organization of US dialysis units, linked with US. Renal Data System records, we used generalized logit models to estimate 12 propensity score (PS) models that addressed combined exposures differently. The 12 models represented all possible combinations of 3 factors: modeling of the exposure (iron only vs. both), coding of the baseline erythropoietin covariate (five levels, three levels, or excluded), and handling of a small group of patients who received no erythropoietin (included or excluded). For each PS we calculated stabilized IPTW and measured balance (standardized differences) across three iron exposure groups.

Results: Mean PS weight ranged from 0.98 to 1.86 across models; maximum weight ranged from 22 to 3,978. The median standardized difference ranged from 0.02 to 0.25 and the maximum ranged from 0.14 to 2.89. Predicting only iron exposure greatly improved weight distribution and balance but ignored erythropoietin exposure. In the models predicting combined exposure, omitting baseline erythropoietin improved weight distribution and balance, even on baseline erythropoietin. Excluding non-recipients of erythropoietin improved neither weight distribution nor balance.

Conclusions: Combined exposures may result in extreme weights or residual imbalance, impeding treatment comparisons. Feasibility assessment should consider the effects of different modeling approaches on weight distribution and covariate balance, as well as the potential for residual confounding.

527. Heterogeneity in Published Evidence for Stroke Prevention in Patients with Atrial Fibrillation: A Systematic Review

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Background: The risk of stroke is approximately five times higher in patients with non-valvular atrial fibrillation (AF). Management with warfarin is associated with increased bleeding events and practical challenges, which may be avoided using novel oral-anticoagulants (NOACs).

Objectives: In order to conduct a robust network meta-analysis (NMA) comparing the efficacy and safety of the NOAC apixaban with comparators of interest, we undertook a systematic review to identify randomised controlled trials (RCTs) evaluating the efficacy and safety of treatments for stroke prevention in AF patients.

Methods: Electronic databases (Cochrane library, Medline, Embase, Biosis and Cinahl; accessed April 20, 2011) and manual bibliographic searches were conducted to identify relevant RCTs. Comparators of interest included other NOACs, vitamin k antagonists (VKA), and aspirin. Relevant data were extracted by two independent reviewers. Key outcomes of interest included stroke or systemic embolism, ischaemic stroke, major bleeding, and all-cause mortality.

Results: In total 46 publications of 41 studies met the inclusion criteria. The majority of studies were multicentre RCTs enrolling warfarin-eligible patients with a low/unknown risk of potential bias. Assumptions of similarity were considered with regards to year of publication, study design (open label vs. double blind), number of enrolled patients, inclusion/exclusion criteria, time in therapeutic range (TTR) and treatments/dosing regimens investigated (particularly among the VKA/aspirin studies). The recently published studies investigating the NOACs were large (>10,000 enrolled subjects), high-quality RCTs

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reporting consistently defined efficacy and safety outcomes.

Conclusions: Use of a restricted RCT network minimises the introduction of unnecessary heterogeneity into a meta-analysis. However, important methodological differences still exist between the published NOAC trials which may introduce a potential for variable interpretation. In the absence of head-to-head studies, a robust assessment of the relative efficacy/safety of the NOACs remains challenging.

528. Disease Risk Scores (DRS) as a Confounder Summary Method: Systematic Review and Recommendations

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Background: Disease Risk Scores (DRS) are confounder summary scores based on the predicted risk of disease outcome and may be advantageous over other confounding adjustment techniques when: (1) exposure is rare, (2) studying multiple exposure categories; and (3) to study effect modification by outcome risk.

Objectives: To systematically examine the trends and applications of DRS confounder summary score methods in the medical literature.

Methods: We conducted a systematic search of MEDLINE and Web of Science® to identify all English language articles that applied DRS methods. We tabulated the number of publications by year and type (empirical application, methodological contribution, or review paper) and summarized methods used in empirical applications overall and by publication year (< 2000, 2000 +).

Results: Of 714 unique articles identified, 98 were eligible, and 86 were empirical applications. We observed a bimodal distribution in the number of publications over time, with peaks in 1979–1980, and then resurgence since 2000. The majority of applications derived DRS using logistic regression (42%), used DRS as a categorical variable in analyses (79%), and were applied in cohort (47%) or case-control (42%) settings. The greatest area of growth was in pharmacoepidemiology, with 46% of applications since 2000 vs. 6% before 2000 examining drug exposure. Few studies examined effect modification by DRS strata (outcome risk).

Conclusions: Use of DRS has increased yet remains low. Comparative effectiveness research may benefit from more DRS applications, particularly to examine effect modification by outcome risk. More research is needed to support use of DRS in case-control studies. Standardized terminology may facilitate identification, application, and comprehension of DRS methods.

529. Health Status to Policy Advocacy and New Drug Licenses

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Background: In Thailand, the burden diseases are cancer, hypertension, heart,cerebrovascular, and infectious diseases. Most of them are preventable.The priority health policy advocated for behavior change by healthy promotion and unhealthy prevention.Treatments and drugs are still important and there should be enough supplied for all the people. FDA is responsible for drugs approval. It should be clarify whether new drugs served for the health policy advocacy.

Objectives: To described and verified new drugs licenses for treating the priority burden diseases.

Methods: New drugs licenses approved from 1/1/2009 to 6/30/2010 were used for analysis of therapeutic uses along with their frequency to priority burden diseases. We used all ADRs reports, received in 2008, for classification of their drug groups.

Results: Three hundred and sixty two new drugs were identified. Of these, 77% were for therapeutic use for cardiovascular disease (i.e., hypertension, diabetes). Anti-cancer, anti-infective, and central nervous disease, are 70%, 68%, and 60%, respectively. One new drug was registered for lifestyle use (erectile dysfunction). Suspected drugs, totaling 38,698, according to ADRs reports were classified by drug group. The most suspected drug group is anti-infective, which constituted more than half of all (52%). Musculoskeletal system is the second, 17%, followed by central nervous system 11%, and others.

Conclusions: 1. Most new drugs have met the needs of burden diseases. On the other hand, of the many new drugs for lifestyle use that were registered, too many of these new drugs are for preventable diseases such as diabetes, depressant, or even HIV AIDS.

2. The most ADRs reports came from anti-infective drug group. The others are areas such as central nervous, cardiovascular, etc. As it has been said, no drug is inherently safe. A person taking a drug is exposed not only to the likely benefits of treatment, but also the risks of unwanted effects, ADRs.

3. Evidence based on burden diseases, ADRs, and new drugs license approval should be used primarily for setting health policy. Accordingly, involved organization should translate policy to action effectively.

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530. Safety Evaluation of Generic and Brand-Name Products of Ampicillin Sodium/Sulbactam Sodium for Injection

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Background: The consumption of generic drugs of parenteral antibiotics is increasing more than ever because of cost consciousness. However there are only a few reports to compare safety of generic with brand-name drug used in infectious disease.

Objectives: We compared safety of generic with brand-name drug of SBT/ABPC for injection at a special functioning hospital.

Methods: This was a retrospective, cross-sectional study of medical records. The original brand-name product was administered to patients in the general ward, in the contrast the generic product to patients in the emergency ward. In order to adjust the confounding factors caused by the patient backgrounds, the patients were matched according to sex, age (younger or older than 65 years), and duration of drug administration (57 or 814 days). The degree and frequency of adverse reactions were compared on that basis.

Results: The number of cases was 52 each after the matching. The percentage of cases which were administered the other parenteral antibacterial agents because of ineffectiveness or adverse reactions were 11.5% for the original brand-name product and 25% for the generic product. The percentage of adverse reactions or abnormal clinical test results was 21.1% for the original brand-name product and 34.6% for the generic product. The results were not significantly different from each other but numerous trends related to adverse reactions were observed in the generic product drug. However drug-induced fever was suspected in 3 patients who experienced a decrease in body temperature after ceasing administration the generic product. Furthermore, two among four patients whose C-reactive protein (CRP) levels increased by >15 mg/L were suspected to be suffered from drug-induced fever from a clinical viewpoint.

Conclusions: We should carefully monitor the clinical data with the possibility of drug-induced fever in mind after switching to a generic or brand-name product depending on the situation, especially in infectious disease.

531. Abstract withdrawn by author.

532. Performance of Overall vs. Subgroup Propensity Scores When an Important Subgroup Variable Is a Strong Confounder

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Background: Propensity scores (PS) reduce bias due to non-random treatment assignment in observational studies. In subgroup analyses, there may be efficiency and validity gains in deriving separate subgroup PS compared to one PS for the total study population, especially if the channeling of treatments likely varies across subgroups.

Objectives: In type 2 diabetes patients (T2D) with or without prior cardiovascular disease (CVD), we compared the risk of nonfatal myocardial infarction (MI) between initiators of sulfonylurea (SU) or metformin (MET) using overall and subgroup PS.

Methods: We conducted a retrospective cohort study using 2006–2009 Medicare (Part A,B,D) data. The study population was T2D patients >65 years, initiating SU or MET monotherapy. PS in the total study population (overall) and within prior CVD strata (subgroup PS) were derived based on a priori list of confounders. We used 5–1 decimal 1:1 PS matching along with Cox proportional models to estimate hazard ratios (HR) and 95% confidence intervals(CI) for MI in an intent to treat analysis.

Results: Of 75,762 patients with mean age 74 years initiated SU (36.7%) and MET (63.3%) therapy; 58.5% were women and 50.7% had prior CVD. During 426 days of median follow-up there were 1244 MIs. With overall PS, MET initiator matches were found for 58% and 71% of SU initiators with and without prior CVD, respectively. Using subgroup PS, corresponding numbers increased to 83% and 94%. In those without prior CVD, no important MI risk factors (e.g., hypertension) were imbalanced after matching on overall PS and the HRs using overall PS (HR = 1.4,CI:1.2–1.8) and subgroup PS (HR = 1.3, CI:1.1–1.6) differed by 7%. In those with prior CVD, the HRs using overall PS (HR = 1.6,CI:1.4–1.8) and subgroup PS (HR = 1.6,CI:1.4–1.9) did not differ.

Conclusions: Matching on overall or subgroup PSs produced similar HR estimates in patients with and without CVD but a larger proportion of SU initiators could be matched based on subgroup PSs. Additional data using stratification, inverse probability treatment weighting, comparing covariate balance using average standardized mean difference and change in estimate approach will be presented.

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533. Beware of Policy-Induced Selection Bias in Drug Effect Studies: Example in the Comparative Effectiveness of Oral Bisphosphonates

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Background: Oral bisphosphonates are effective in reducing vertebral fracture risk, however, only alendronate and risedronate have proven efficacy in reducing hip fracture risk.

Objectives: To examine the comparative effectiveness of cyclical etidronate and risedronate vs. alendronate in reducing hip fracture risk among older men and women.

Methods: We examined the comparative effectiveness of oral bisphosphonates in reducing hip fracture risk among new users aged 66 or more years in British Columbia (BC) and Ontario, 2001/02–2008/09. BC data included all drugs dispensed in community pharmacies. Ontario data included drugs covered through the public plan that openly listed etidronate therapy, yet largely restricted alendronate and risedronate to those with lower bone mineral density. Medical claims were complete for all residents in both provinces. Sex- and province-specific Cox-proportional hazards models, matched on propensity score, were used to compare 1-year hip fracture rates between exposures. Propensity scores were derived using risk factors for hip fracture from healthcare utilization data. Alendronate was the referent in all comparisons.

Results: We identified little difference in fracture rates between etidronate or risedronate and alendronate among men and women in BC, or among women in Ontario. We similarly identified little difference in fracture rates between risedronate and alendronate (HR = 0.94; 95%CI = 0.79–1.16) among men in Ontario. However, we identified lower hip fracture rates among men in Ontario treated with etidronate vs. alendronate (HR = 0.75; 95%CI = 0.59–0.95).

Conclusions: We identified little difference in the effectiveness of alendronate or risedronate in reducing hip fracture risk among men or women. Despite being matched on measured risk factors for fracture, results suggest that residual confounding persisted with fracture rates lower among men in Ontario treated with etidronate compared to alendronate. Careful attention to province-specific drug restriction policies in Canada is important when examining the comparative safety and effectiveness of medications.

534. Methodological Considerations in Estimating Drug Adherence for a Long-Acting Injectable Medication

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Background: Drug adherence has been shown to lower health care use and costs (Roebuck, 2011). Adherence measures are established for oral medications using prescription claims data; however, application of such measures to long-acting injectable agents is less understood.

Objectives: To compare standard measures of adherence for long-acting and orally-administered second generation antipsychotics (SGA) to determine whether the findings are consistent between measures.

Methods: This was a retrospective new user cohort study of claims data from Missouri Medicaid (08/09–04/11). The study population was adults (18–64 year) diagnosed with schizophrenia. Follow-up was 12 months. We identified new starts of paliperidone palmitate, a long-acting SGA (LA-SGA) dosed once monthly (n = 248) and the most commonly used oral SGA, aripiprazole (O-SGA) (n = 179). Adherence measures calculated from pharmacy claims were: medication possession ratio (MPR, 0–1.0) and percent days covered (PDC, 0–100%). We also looked at clinically meaningful gaps between refills (Sikka, 2005). Due to differences in product formulation, the threshold for the maximum allowable gap was set based on average product half-life [3 days (O-SGA) and 37 days (LA-SGA)] as a proxy for duration of therapeutic drug levels. Student's *t*-test and χ^2 tests were used to compare cohorts.

Results: Mean (standard deviation) prescriptions per patient were 8.1 (4.6) and 6.2 (4.9) for the LA-SGA and O-SGA respectively, $p < 0.01$. Mean MPR did not differ between LA-SGA and O-SGA (0.83 vs. 0.82, $p = 0.68$). Mean PDC was higher for the LA-SGA than O-SGA group (55% vs. 42%, $p < 0.01$). The proportion of patients with no gap in therapy exceeding the maximum gap threshold was higher for patients in the LA-SGA vs. O-SGA cohort (73% vs. 35%, $p < 0.01$).

Conclusions: Standard drug adherence measures yielded different conclusions when comparing a long-acting and oral antipsychotic medication. Valid adherence measures

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which address pharmacological differences in terms of duration of therapeutic levels between drugs are necessary. Until then, investigators should consider sensitivity analysis using different adherence definitions when making product comparisons.

535. Geospatial Variations in Drug Utilization and the Potential for Confounding by Geography

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Background: Regional variation in health service utilization and diagnostic practices has been demonstrated in administrative data sets. Geographic differences in drug use could confound observational drug studies comparing health service outcomes.

Objectives: To estimate geographic variation in drug utilization using antipsychotics as the case example.

Methods: A retrospective cohort study was conducted with claims data from Missouri Medicaid (August 2009-April 2011). Three new user cohorts were identified: oral atypical antipsychotics (AA-Oral) (N = 109,173); paliperidone palmitate, a long-acting injectable AA (AA-LAI) (N = 1,531); and conventional long-acting injectable antipsychotics (C-LAI) (N = 2,506). Spatial Empirical Bayes smoothing was used to calculate and map rates of prescription claims (per 10,000 pop) for each cohort by patient ZIP Code. The Moran's I statistic was used to test for the presence of global spatial autocorrelation. Local indicators of spatial clustering (LISA) were calculated and mapped to examine the presence of clusters of mutually similar deviations from the overall mean rate. Monte Carlo simulation (N = 999 permutations) was used to calculate p-values for the probability of observing higher or lower prescribing clusters.

Results: Drug use patterns varied qualitatively between cohorts. The Global Moran's I indicated a strong positive spatial clustering pattern for AA-Oral use (I = 0.2536; $p < 0.01$) and moderate positive spatial clustering for AA-LAI (0.1287 ($p < 0.01$) and C-LAI (I = 0.1319; $p < 0.01$) use. LISA maps showed large clusters of greater AA-Oral use ($p = 0.01$) in the rural SE corner of the state and lower rates ($p = 0.01$) in three major urban areas. LISA maps showed smaller geographic clusters of AA-LAI use ($p = 0.05$ and $p = 0.01$) along a NW-to-SE diagonal line across the state. A few small pockets of ZIP codes with high rates of C-LAI use were found ($p = 0.01$).

Conclusions: Significant geographic variation in drug use was observed between cohorts of new users of antipsychotics. An investigation of geographic variation in mental health services (e.g., hospitalizations) is under way to estimate the magnitude of potential confounding by geography.

536. Evaluating Effects of Changing Treatments in Longitudinal Studies

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Background: In studies evaluating treatment effects for endpoints such as overall survival, patients are expected to change treatments during follow-up due to disease progression, adverse events, or other reasons. It is often of interest to compare efficacy endpoints across the entire treatment pattern, assessing the effects of the sequence of initial treatments and second- or even third-line treatments. However, in practice, researchers often either ignore second-line treatments or simply stratify patients by whether they received second-line treatment. These simplistic approaches have a purpose but do not take full advantage of the longitudinal information. The use of time-varying covariates in Cox models can provide valuable insights into treatment sequencing, for example, in oncology research. However, these methods are not used widely even in situations where they are clearly applicable; the intent of this presentation is to highlight the usefulness of survival analyses that assess time-varying covariates.

Objectives: To appropriately account for second-line treatment when evaluating the effect of first-line treatments and to evaluate the effect of second-line treatments.

Methods: We constructed Cox models for time-to-event endpoints with second-line treatments handled as time-varying covariates.

Results: We first illustrate why commonly used methods are not always appropriate. Next, we show how the time-varying covariates for treatments work in practice when additional treatments are received after the initial treatment, focusing on interpretation of results. We show different model settings that reflect various clinical assumptions. Finally, we discuss other applications, considerations, and assumptions when using time-varying covariates.

Conclusions: The technique of incorporating time-varying covariates in analyses of time-to-event endpoints provides a flexible analysis method to evaluate treatment effects in complex situations in which patients receive a sequence of treatments. This approach has wide applications, most notably in oncology research.

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537. Time-Dependent Propensity Score and Collider-Stratification Bias: Inhaled beta2-Agonist and Risk of Coronary Heart Disease

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Background: In observational studies of time-varying exposure and confounders, the use of propensity score (PS) is limited to assigning weights as in marginal structural models (MSMs). Stratification and conditioning on time-varying cofounders which are also intermediates can induce collider-stratification bias and adjust-away the (indirect) effect of exposure. Similar bias could be expected when one conditions on time-dependent PS.

Objectives: We explored collider-stratification and confounding bias due to conditioning or stratifying on time-dependent PS in a clinical example on the effect of inhaled short and long-acting beta2-agonist use (SABA and LABA, respectively) on coronary heart disease (CHD).

Methods: A cohort of patients with an indication for SABA and/or LABA use was extracted from the Netherlands University Medical Center Utrecht General Practitioner Research Network. Information from 1995 to 2005 was used. SABA and LABA use and potential confounders were ascertained on 3 month intervals. Follow-up began the first day of diagnosis of bronchitis, asthma, or COPD and ended at the occurrence of CHD, death, unregistration with the GP, or end of the study, whichever occurred first. HR were estimated using PS stratification as well as covariate adjustment and compared with those of MSMs in both SABA and LABA separately. In MSMs, censoring was accounted for by including inverse probability of censoring weights.

Results: The crude HR of CHD was 0.90 [95% CI: 0.63, 1.28] and 1.55 [95% CI: 1.06, 2.62] in SABA and LABA users respectively. When PS stratification, adjustment using PS, and MSMs were used, the HRs were 1.09 [95%CI: 0.74, 1.61], 1.07 [95% CI: 0.72, 1.60], and 0.86 [95% CI: 0.55, 1.34] for SABA, and 1.09 [95%CI: 0.74, 1.62], 1.13 [95%CI: 0.76, 1.67], 0.77 [95% CI: 0.45, 1.33] for LABA, respectively.

Conclusions: Results were similar for different PS methods, but systematically higher than those of MSMs. When treatment and confounders vary during follow-up, conditioning or stratification on time-dependent PS may induce substantial collider-stratification or confounding bias. Hence, the use of methods such as MSMs is recommended.

538. Change in Exposure in Studies of Chronic Conditions: Insights from a Mixed Effects Multinomial Logit Model

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Background: In studies of treatment of chronic conditions, patients often change exposure status over follow-up. Patients may switch or discontinue drugs, or change drug class or dose. Assessment of drug effectiveness or safety requires that we account for the time-dependent nature of exposures, and that we understand determinants of exposure change.

Objectives: Demonstrate use of the statistical tool, the Mixed Effects Multinomial Logit Models in assessing determinants of exposure status change in women with postmenopausal osteoporosis treated with bone loss therapy (BLT).

Methods: A cohort of postmenopausal women registered with the General Practice Research Database (GPRD) treated with BLT between 01/1997 and 12/2008 was constructed (N = 39,341). BLTs were grouped into oral bisphosphonates (OBP) and other (OTH). Change in exposure status included switching from OBP to OTH or OTH to OBP, or discontinuing medication. To account for change in medical practice over time, calendar time was stratified into three periods. For each year within these periods, patients were classified according to the first event (switch or discontinuation). Potential determinants of exposure change were patient characteristics over the 12 months prior to date of switch/discontinuation. For patients without exposure change, characteristics were those over the 12 months prior to 30 June in that year. Multivariable regression models for repeated multinomial response variables (GLIMMIX, SAS 9.2) were used to assess variables associated with medication switch/discontinuation.

Results: Characteristics associated with medication switching or discontinuation included age, arthritis, number of GP contacts (proxy for frailty), osteoporosis duration, BMI, fracture history, and use of glucocorticoids or immunosuppressants.

Conclusions: Multinomial response approaches simultaneously consider risk of multiple events, and thus provide a comprehensive assessment of determinants of change in exposure. By considering successive calendar years, we accounted for the time-dependent nature of determinants, and the mixed effect nature of these models accounts for induced correlation.

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539. Graphical Representation of Confounding Potential for Measured Covariates

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Background: Pharmacoepidemiologic analyses must address potential biases arising from differential distributions of covariates across levels of the exposure of interest. Standard practice for summarizing distributions of covariates is usually the tabular listing of summary statistics for covariates stratified by levels of the exposure. This practice has several limitations for effective representation and evaluation of the complex relationships among measured variables that jointly lead to bias. Visual representation of data can facilitate more accurate and intuitive understanding of the essential information in a complex dataset. Radar charts are a useful way to display multivariate data. We elaborate on the graphical idiom of the radar chart to express multivariate relations among variables in analysis of epidemiologic data, for the purpose of elucidating the aggregate potential for bias.

Objectives: This work proposes a method for graphical representation of the information typically used in assessment of the potential for bias in multivariate analyses. We present applications of the graphic for elucidation of confounding, selection bias, treatment propensity, and randomization balance.

Methods: In this application of the radar plot the spokes denote covariates in the analysis (e.g., baseline patient attributes, concomitant medications, etc.). Intersecting the spokes are lines denoting comparison (treatment or exposure) groups. Where the lines fall on spokes indicates summary value for that group, making comparison of multiple values for a group easy, and facilitating the perception of differences between the groups of interest. Multi-panel conditioning is used for stratifying data and comparing subgroups.

Results: A function has been programmed in the open-source R language to facilitate specification and production of the graph. Applications of this graphic to analysis in various therapeutic areas and analytic issues is presented.

Conclusions: This graphic application is useful for examination of multivariate data, assessment of confounding by measured covariates, selection bias, propensity score modeling, success of randomization, and other activities in epidemiologic analysis and inference.

540. Performance of Instrumental Variable Methods in Case-Control and Cohort Studies: A Simulation Study

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Background: Instrumental variable (IV) methods are becoming increasingly popular to adjust for confounding in pharmacoepidemiological research. IVs are strongly related to the exposure, and only related to the outcome through exposure. When the IV is weak (weak relation with exposure), estimates are likely biased.

Objectives: To assess the bias of IV estimates for different types of exposure, outcome and IV as in case-control and cohort designs.

Methods: Data were simulated for different combinations (continuous or binary) of exposure, outcome and IV using a cohort and a nested case-control (NCC) design with strong confounding. We considered different sample sizes (1,000, 5,000, 10,000 and 50,000) with different incidence of the outcome. Pearson correlation (PC), point biserial correlation (PBC), and odds ratio (OR) were used to measure the strength of the IV. For continuous outcome, the two-stage least squares method was used to estimate the exposure effect. For binary outcomes, linear regression and logistic regression were used in the first and second stage respectively. Bias was defined as the difference between the mean of IV estimate based on 1,000 simulations and the true exposure effect.

Results: The relation between the strength of the IV and bias was similar for different types of IV and exposure and irrespective of the incidence of the outcome. For example, when both IV and exposure were continuous (cohort data) bias was considerable for PC < 0.10, but for PC > 0.10 bias was negligible. For binary IV and continuous exposure (or vice versa) this was observed for PBC $= 0.08$ and when both were binary at OR $= 1.3$. For NCC design these values were 0.20, 0.16 and 1.70 respectively. In addition, the IV estimates were less stable for rare outcome (e.g., 1%), especially in the NCC design.

Conclusions: Similar patterns of bias were identified for all considered scenarios of IV analysis. The IV estimates were unstable for weak instruments or rare outcomes. In such situations, it was not feasible to apply IV methods. In NCC IVs should be stronger than when applying them in cohort studies.

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541. Cardiovascular Risk Factors Associated with Essential Hypertension

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Background: High blood pressure is a public health problem.

Objectives: to determine main cardiovascular risk factors associated with essential hypertension and their distribution by age and sex and place of residence.

Methods: This is a prospective study in November 2010 and February 2012, concerning 742 patients with essential hypertension followed in the outpatient of cardiology, at the city of Rabat.

Results: The mean age was 62.1 ± 11.2 years old. Females were concerned in 65.3% of cases. Complicated hypertension was observed in 58.9% (437). Systolic blood pressure and diastolic blood pressure were 146.16 ± 22.29 and 80.21 ± 12.36 mmHg, respectively. The average body mass index was 28.40 ± 5.75 in men vs. 31.4 ± 8.90 kg/m^2 in women. In 234 women (69.11%), Hypertension was associated with diabetes. Hypertension associated with hypercholesterolemia was found in 46.68% (204) of cases. The association of Hypertension and obesity was significantly higher in females 57.25% (250) and 30.20% (132) in urban areas. Eighty-one per cent of women were passive smokers.

Conclusions: Cardiovascular risk factors associated with hypertension were diabetes, obesity, hypercholesterolemia and smoking. It is necessary to strengthen the action against cardiovascular disease and their cardiovascular risk factors.

542. Antihypertensive Drug Compliance and Its Related Factors in a Korean Population

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Background: Although the level of antihypertensive drug compliance and its related factors are essential elements to improve medication persistence, there have been few studies addressing them in Asian populations.

Objectives: This study aimed to examine the factors associated with antihypertensive compliance in a Korean population.

Methods: Three thousand two hundred thirty-four community dwelling patients aged 20 and over within a defined geographic area participated in this study. Data on antihypertensive drug compliance, socio-demographic factors (age, gender, marital status, education), comorbidities (diabetes mellitus, arthritis) were collected using a structured questionnaire. Logistic regression models were used to determine the factors related to antihypertensive compliance.

Results: Of 84.3% of the patients had good compliance to antihypertensive drugs. Good compliance was associated with advanced age (OR 2.06, 95% CI 1.62–2.62), female gender (OR 1.37, 95% CI 1.07–1.76), low level of education (OR 1.72, 95% CI 1.34–2.22) and comorbidity with diabetes mellitus (OR 1.47, 95% CI 1.09–2.00). In stratified analysis by gender, while the level of education was not associated with good compliance in men, it was associated in women (OR 2.48, 95% CI 1.72–3.57). And in stratified analysis by age group, while the level of education was not associated with good compliance in older group, it was associated in younger group (OR 2.72, 95% CI 1.93–3.83).

Conclusions: Advanced age, female gender, low level of education, and comorbidity with diabetes mellitus were found to be associated with good compliance to antihypertensive drugs in a Korean population. The association between education and antihypertensive compliance was modified by age and gender.

543. Risk of Acute Myocardial Infarction (AMI), Stroke, or Death in GPRD Patients Treated with Olmesartan (Olm) or Other Angiotensin Receptor Blockers (ARBs)

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Background: Results of two randomized trials (ROADMAP and ORIENT) suggested that Olm increased cardiovascular (CV) mortality compared to placebo in diabetic patients.

Objectives: We evaluated the risks of AMI, stroke, sudden cardiac death (SCD), and all cause mortality, after initiating Olm compared with other-ARBs to study the association between Olm and CV-related events.

Methods: We conducted a cohort study using the UK GPRD. Patients (40–95 years of age) with at least one Olm or other ARB prescription during the study period January 2003–June 2011 were included. Index date (t_0) was set to the first prescription date. To qualify for inclusion in the cohort, patients had to be in the practice for 12 months prior to t_0, and have no prescription for any ARB or angiotensin converting enzyme inhibitor (ACEI)

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for 6 months prior to t_0 (new users). A patient was followed from t_0 until the earliest of (1) a gap in treatment coverage >25% of the prior prescription days' supply; (2) a prescription fill for a different ARB or ACEI (switching); (3) the occurrence of an outcome; (4) the end of the study period; or (5) the end of available data. AMI was previously validated. We randomly selected 1,000 stroke and 1,000 SCD cases for validation. Hazard ratios (HR) of CV-related outcomes and mortality will be estimated using Cox proportional hazard models adjusting for CV-related risk factors.

Results: There were 3,964 Olm initiators and 54,653 other-ARBs initiators, who fulfilled all inclusion criteria. The mean patient age was 65 years (SD = 12) for the Olm cohort, and 66 years (SD = 12) for the other-ARBs cohort. Cohorts included 55.8% and 56.1% females, respectively. The mean follow-up duration was 390 days (SD = 524) for the Olm cohort, and 425 days (SD = 560) for the other-ARBs cohort. Overall, there were 0.5% and 0.6% new users who developed AMI or stroke, with 1.2% who died during the follow-up period.

Conclusions: The Olm cohort and the other-ARBs cohort are generally similar regarding patient characteristics. Validation results and adjusted HR will be reported.

544. The Effect of Statins on the Risk of First Non-Fatal Myocardial Infarction: A Population-Based Observational Study Using the PGRx Information System

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Background: Despite demonstrated positive effects in a number of clinical trials, the evidence is lacking as to the impact of statins on the risk of first myocardial infarction (MI) in real life settings.

Objectives: To assess the impact of real life statin utilization on the risk of first non-fatal MI.

Methods: Case–Control methodology using the pharmacoepidemiological information system "PGRx". Data on comorbidities, risk factors and medications were obtained from medical records and patient telephone interviews. General practices (n = 371) and cardiology centres (n = 60) across France were employed in the study. Cases were patients with the first MI ≤ 1 month before the date of recruitment (n = 2238). Controls were patients seen by a general practitioner (GP) with no restriction as to the reasons of consultation (n = 2238), matched to MI cases on gender, age, frequency of visits to a doctor, date of recruitment and personal history of non-cardiovascular chronic disease. Statin exposure was defined as any utilisation in the 2-year prior to date of MI in cases or recruitment date in controls. Adjusted odds ratios (OR) of the risk of first MI was estimated by multiple conditional logistic regression models. Comparative effectiveness and propensity to use of individual statin molecules were assessed.

Results: The use of statins was associated with a lower MI risk (adjusted OR 0.67 [95% CI 0.56–0.79] for current use (within 2 months before the index date) and 0.73 [0.62–0.86] for any use within 24 months). Among individual statins, rosuvastatin was associated with the lowest MI risk (adjusted OR 0.49 [0.35–0.68] for any use in 24 months preceding the index date) followed by simvastatin (0.62 [0.46–0.84]).

Conclusions: In this first major population-based observational study we reproduced the results observed in recent meta-analyses accounting for real life compliance and population variability. The results could be of interest and applicable to other industrialised countries as the observed risk reduction was constant across MI risk levels.

545. Use of Low Dose Aspirin Increased Cardiovascular Risk in Incident Diabetic Patients

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Background: Aspirin is recommended to reduce the risk of cardiovascular diseases (CVDs) in diabetic patients. However, questions have been raised about the effectiveness of primary prevention of CVDs and the potential risk of increased bleeding aspirin may pose for diabetic patients.

Objectives: To evaluate the effectiveness of low dose aspirin use in preventing CVDs in newly diagnosed diabetic patients.

Methods: Using the Korean Health Insurance Review and Assessment Service database, a retrospective cohort of patients ≥40 years of age, newly diagnosed with diabetes (ICD-10, E10-14) between January 2006 and December 2007, were included. We excluded patients with

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diabetes during the year before index year or with CVDs before the index date. Patients were received low dose aspirin (≤200 mg) prescriptions in index year 2006, 2007 as an exposure group compared with non-users. The follow-up endpoint was defined as hospitalization with CVDs including angina (I20.x), acute myocardial infarction (AMI; I21.x, I22.x, I23.x), ischemic stroke (IS; I63.x, G45.x) and coronary revascularization, death or the end of the study (December 31st, 2009). Cox proportional hazards model was used to evaluate effects of aspirin on incidence of CVDs after adjusting for possible confounding factors (hypertension, dyslipidemia, and use of CV related medications).

Results: The cohort included 268,489 newly diagnosed DM patients, among them, 22,707 (8.4%) were prescribed low dose aspirin. The adjusted hazard ratio for low-dose aspirin user compared with non-user was 2.13 (95% CI: 1.97–2.30) for AMI; 1.37 (95% CI: 1.25–1.49) for IS; and 1.73 (95% CI: 1.64–1.83) for the all CVDs.

Conclusions: In this study of diabetic patients, low aspirin use increased the risk of CVD events. It may provide evidence for revising clinical guidelines that recommend cautious use of low dose aspirin to prevent CVDs in incident diabetic patients.

546. Long-Term Compliance to Acetylsalicylic Acid in Patients after Acute Coronary Syndrome

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Background: Acetylsalicylic acid (ASA) is widely used for prevention of cardiovascular events (CVE). Compliance as the major effectiveness determinant in preventive acetylsalicylic acid therapy.

Objectives: To estimate the long-term compliance to ASA in patients after acute coronary syndrome (ACS).

Methods: The prospective observational study included subjects aged at least 18 years who had ACS. Compliance to ASA was estimated by the questionnaire survey. Statistical analysis included calculations of percentages for discrete variables, means and standard deviations (SD) for continuous variables, logistic regression analyses. Statistical significance was set at an accepted alpha ($p < 0.01$).

Results: The study population included 757 patients after ACS – 408 (53.9%) men and 349 (46.1%) women, with a mean age of 62.1 ± 7,6 years. Of 39.2% of patients received buffered ASA, 42.7% – enteric-coated ASA (EC ASA), 18.1% – plain ASA. Compliance to ASA was assessed by a 10-point visual analog scale. Only 16.2% of patients were adherent to ASA (10 points). Patients who received EC ASA were significantly more adherent to long-term therapy than patients who received buffered ASA and plain ASA (8.4 ± 1.4, 7.6 ± 1.4 and 7.0 ± 1.6 points respectively, $p < 0.01$). Of 81.6% of patients discontinued the treatment of ASA. Patients who received buffered ASA and plain ASA, were significantly more likely than patients who received EC ASA, discontinued the treatment (respectively OR = 1.81; CI [1.20–2.72], $p = 0.0027$ and OR = 4.86; CI [3.01–7.85], $p = 0.0003$). The main factor for discontinuation therapy was development of adverse reactions (52.8%). Patients received EC ASA, discontinued the treatment due to development of adverse reactions significantly less likely than patients who received buffered ASA (OR = 0.49; CI [0.35–0.69], $p = 0.00002$), and plain ASA (OR = 0.21; CI [0.13–0.33], $p = 0.00001$).

Conclusions: Of 81.6% of patients after ACS had low compliance to long-term ASA therapy. The main reason for discontinuation ASA was development of adverse reactions. Patients who received EC ASA were significantly more adherent to long-term therapy than patients who received buffered and plain ASA.

547. Diuretics and the Risk of Developing Gout

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Background: Gout is a common rheumatic disease in humans which is characterized by elevation in serum uric acid levels, deposition of uric acid crystals in the joint, and an acute inflammatory arthritis. While current use of diuretics is discussed to increase the risk of developing gout, the impact of different groups of diuretics is largely unknown.

Objectives: We aimed to study the association between the use of different types of diuretics and the risk of developing gout.

Methods: We conducted a Case–Control study on the UK-based General Practice Research Database (GPRD). We identified cases aged between 18 and 80 years with an incident gout diagnosis between 1995 and 2009 and matched them to one control patient on age, sex, general practice, calendar time, and years of history in the database. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of developing gout in relation to previous use of different groups of diuretics such as thiazide diuretics, thiazide-like diuretics, and loop diuretics prior to the index date between cases and controls, stratified by timing of use and adjusted for potential confounders.

Results: The study encompassed 91,530 cases with a first-time gout diagnosis and the same number of controls. As compared to non-users, current users of diuretics were at an increased risk of developing gout (adjusted OR 2.08,

95% CI 1.98–2.21). Adjusted OR for current use of loop diuretics, thiazide-like diuretics and thiazide diuretics was 2.90 (95% CI 2.74–3.06), 2.45 (95% CI 2.21–2.73), and 1.80 (95% CI 1.73–1.88), respectively.

Conclusions: This analysis suggests that patients with diuretics are at increased risk for incident gout. Loop diuretics seem to have the biggest impact, followed by thiazide-like diuretics and thiazide diuretics.

548. Secondary Prevention Drugs Following Acute Myocardial Infarction after Hospital Discharge, 6 and 24 Months Thereafter: Results from the EOLE Cohort

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Background: Use of drugs for secondary prevention after acute myocardial infarction (AMI) is recommended by international cardiology societies.

Objectives: The objective of this analysis was to estimate the use of the drugs recommended following AMI after hospital discharge, at 6 months, and at 24 months of follow-up.

Methods: A cohort study was designed to include 5,000 patients with recent AMI (< 3 months) recruited by hospital and non-hospital cardiologists. At inclusion, drug exposure was assessed from physician and patient declarations. At 6 months and at 24 months, it was assessed from patient declaration.

Results: Between May 2006 and June 2009, 5,538 patients were included. Follow-up drug exposure was available for 3,348 patients (60.5%) at 6 months, 3,763 (67.9%) at 24 months. The baseline characteristics of analysed populations were similar to those of included patients. Mean age was 62.1 years, 77.6% were male, 9.6% current smokers, 16.7% had diabetes, 44.6% hypercholesterolemia, 43.6% high blood pressure. For 86.7%, it was the first AMI, 70.5% had all three AMI criteria (symptomatic, electrical, enzymatic), 8.2% had LVEF < 40%. At inclusion, 99.4% of patients were exposed to aspirin or other anti-platelet agents, 95.8% statins, 89.7% beta-blockers, 73.8% angiotensin-converting enzyme inhibitors (ACEi). Exposure to the recommended combination of these four treatments (BASI) was 65.7% at inclusion, 57.1% at 6 months (initiation after inclusion: 4.3%), 50.3% at 24 months (initiation after inclusion: 5.5%). Persistence of exposure to the BASI treatments from inclusion was 79.3% at 6 months, and 66.8% at 24 months. Omega-3 supplementation, also recommended, was 15.7% at inclusion, 17.5% at 6 months (initiation after inclusion: 3.4%), 16.0% at 24 months (initiation after inclusion: 4.4%). Omega-3 supplementation persistence was 82.4% at 6 months, 68.2% at 24 months.

Conclusions: Long-term persistence to the BASI treatment combination only concerned two-thirds of patients. The reasons for this remain to be elucidated in an attempt to improve use of this recommended drug regimen. Furthermore, omega-3 supplementation was not frequent.

549. Use of Allopurinol and Risk of Myocardial Infarction: A Case–Control Study

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Background: While gout is considered as a risk factor for vascular diseases, the relation of allopurinol with the risk of cardiovascular events is controversial. In some studies, drug use was associated with an increased vascular risk, while other studies described a protective effect.

Objectives: We conducted a case–control study to examine the relation between allopurinol use and risk of myocardial infarction (MI).

Methods: Cases (n = 2277) were successive patients with a first-ever non-fatal myocardial infarction referred to 63 cardiology centres throughout France between March 15, 2007 and November 30, 2010. They were matched to 2,277 controls selected in a large (12,313) general practice patient referent population. Controls had no past history of coronary heart disease and were matched to MI cases on age, gender, number of visits to a doctor in the preceding year, date of consultation (MI) and past history of high blood pressure. Data about medication use during

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the two preceding years, and past medical history and life habits (smoking, physical activity, etc.) were obtained from patient's standardized interview and GP records. Odds ratios (OR) and their 95% confidence interval were computed using conditional logistic regression, adjusting for classical vascular risk factors (body mass index, smoking, diabetes, physical activity).

Results: MI cases and controls had a mean age of 59 years, 76% were men and 56% reported a history of high blood pressure. High body mass index, low physical activity, smoking and diabetes were more prevalent in cases than in controls, whereas controls reported regular alcohol consumption more frequently than cases. Overall, during the two preceding years, 4% of controls and 3.1% of MI cases had used allopurinol, and 1.1 of both cases and controls had used another hypouricemiant. Use of allopurinol was associated with a non significant decreased risk of MI (adjusted OR [95% CI]: 0.76 (0.54–1.06).

Conclusions: This study showed that allopurinol use is not a risk factor for first-ever non-fatal MI and might rather be associated with a decreased risk of MI.

550. Spironolactone and the Risk of Breast Cancer: A Cohort Study

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Background: Spironolactone is increasingly being prescribed long-term for cardiovascular conditions such as heart failure and resistant hypertension. Due to its breast side effects (gynaecomastia and breast tenderness) and anti-androgenic and progestogenic actions, there has been concern that its use could increase the risk of breast cancer.

Objectives: To determine whether spironolactone use increases the risk of incident breast cancer in women. The a priori hypothesis was that spironolactone may increase the risk of breast cancer.

Methods: The study was an observational matched cohort study of time to events of breast cancer in a cohort exposed to spironolactone (two or more prescriptions) and a non-exposed cohort in the General Practice Research Database (GPRD) – a UK primary care anonymised database representative of the general population. The study included women over 55 years of age. The study population consisted of 1,290,625 patients from 557 practices with a total follow-up time of 8.4 million patient years. The main outcome measure was new cases of breast cancer.

Results: There were 29,491 new cases of breast cancer in the study population, an incidence rate 0.35% per year in women aged at least 55 with no prior history of breast cancer. In a cohort of 28,032 patients exposed to spironolactone and a cohort of 55,961 unexposed patients matched on year of birth and followed up from the same date, the unadjusted incidence rates were 0.39% and 0.38% per year respectively. Time to event analysis, adjusting for potential risk factors, provided no evidence of an increased incidence of breast cancer in patients exposed to spironolactone (hazard ratio 0.99, 95% CI 0.87–1.13).

Conclusions: These data provide reassurance that the long-term management of cardiovascular conditions in women with spironolactone does not increase the risk of breast cancer.

551. Use of Fibrates and Risk of Cancer: Results from a Nested-Case–Control Study

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Background: An increased risk of bladder cancer has been associated with the use of pioglitazone, which acts on PPARα, as do fibrates.

Objectives: To study the association between fibrate use and risk of cancer of tissues highly expressing PPARα.

Methods: A nested Case–Control study was conducted within the "Echantillon Generaliste des Beneficiaires" cohort (EGB), a random 1/97 sample of the French national healthcare insurance system reimbursement database. All subjects aged ≥45 years included in the EGB and free of cancer on 01/01/2004, and who did not exit except in case of death were eligible. Cases were defined as patients with incident recording of bladder, kidney, pancreas, skin (melanoma/other malignant), and thyroid cancer between 01/01/2007 and 31/12/2007. Incidence density sampling was used to obtain up to 10 random controls per case, matched for year of birth (± 1 year), sex, and history of coronary heart disease, COPD, chronic liver disease, diabetes, heart failure, HIV, and schistosomiasis. Index date was that of first diagnostic record for cases and that of sampling for controls. Exposure to fibrates was measured using reimbursement data for the follow-up period up to six months before index date. Conditional logistic regression was used to estimate the association between fibrate use and risk of cancer, adjusted on use of aspirin, statins, biguanides, sulfonamides, pioglitazone, and other antidiabetics.

Results: Nine hundred and sixty-nine cases were identified, who were matched to 9,571 controls. Cancers of the bladder, kidney, pancreas, skin, and thyroid accounted

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for 30.6, 15.8, 17.9, 27.3, and 8.6% of cases, respectively. Patient mean age was 69.9 years (SD: 11.0), 56.6% were male; 18.3% of cases and 14.9% of controls were exposed to fibrates. Among all those exposed, median fibrate use was 605.3 DDDs (IQR: 181–1220). After multivariate analyses, the Odds Ratio of the association was estimated at 1.2 (95% CI: 0.9–1.6) for fibrate use < 600 DDDs, and at 1.4 (95% CI: 1.1–1.8) for fibrate use ≥600 DDDs.

Conclusions: An increased risk of cancer for tissues highly expressing PPARα was found in fibrate users with ≥600 DDDs of exposure.

552. Cardiovascular Diseases and Drugs and the Risk of Developing Rosacea

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Background: Rosacea is a skin disease, presumably partly of vascular origin. The microvascular function of the skin can correlate with cardiovascular (CV) changes (e.g., blood pressure). Hence, CV diseases or drugs might affect skin perfusion and therefore the risk of developing rosacea. Despite scarce and/or contradictory evidence, beta-blockers (BBs) have been linked to lower rosacea risks, whereas calcium channel blockers (CCBs, especially dihydropyridines) and hypertension have been discussed as risk factors. We are not aware of any studies on rosacea in association with other CV diseases or with ACE-inhibitors (ACEIs), AT2-antagonists (AT2As), or statins.

Objectives: To analyze the association between CV diseases and drugs (excluding diuretics) and the risk of incident rosacea.

Methods: We conducted a matched case–control analysis using the UK-based General Practice Research Database. We included cases with an incident rosacea diagnosis between 1995 and 2009, and compared the prevalence of CV diseases and the exposure to CV drugs prior to the index date between cases and controls.

Results: We identified 60,042 rosacea patients and the same number of controls. Most CV diseases revealed odds ratios (ORs) around unity. Hypertension and myocardial infarction revealed slightly decreased adjusted ORs of 0.86 (95% CI 0.82–0.90) and 0.83 (95% CI 0.75–0.92), respectively. Use of ACEIs, AT2As, statins, and BBs had no impact on the risk estimate. After stratifying CCBs into dihydropyridines (causing vasodilatation) and non-dihydropyridines, we found a significantly decreased adjusted OR of 0.73 (95% CI 0.55–0.96) for current long-term use of dihydropyridines (40 + prescriptions/last prescription < 180 days), whereas long-term use of non-dihydropyridines yielded an OR around one.

Conclusions: BBs revealed a null result, although they have been suggested as an off-label treatment for rosacea. The decreased OR of long-term use of dihydropyridines and the null result for non-dihydropyridines contradict the hypothesis of an increased rosacea risk of these drugs. Myocardial infarction and hypertension were associated with slightly lower rosacea risks, but residual confounding might have played a role.

553. Confounding Adjustment in a Distributed Data System without Sharing of Individual-Level Data

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Background: It is increasingly common for studies to analyze multiple datasets, but concerns about privacy and security often reduce data holders' willingness to share detailed individual-level data.

Objectives: To evaluate two approaches that do not require sharing of individual-level data to adjust for multiple confounders in a distributed data system in which data reside physically at each site.

Methods: We estimated the risk of angioedema among new users of angiotensin converting enzyme inhibitors (ACEIs, n = 1,845,138), angiotensin receptor blockers (ARBs, n = 467,313), and the renin inhibitor aliskiren (n = 4,867) compared to new users of ß-blockers (n = 1,592,278). We used the case-centered logistic regression approach developed by Fireman to combine data from 17 Data Partners in the Mini-Sentinel program. The approach fit a logistic model using data from an aggregate dataset that included one record per risk set. In the ACEI analysis, for example, the outcome variable was whether the angioedema case was exposed to an ACEI; the independent variable – specified as an offset in the model – was the log odds of the site-specific proportion of ACEI users in the risk set comprised of individuals belonging to the same propensity score (PS) quintile as the case. The model also included site as a stratification variable. This model has been shown to produce the same results as a stratified Cox model fit using individual-level data. The second approach combined site-specific hazard

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ratios (HRs) obtained from PS-stratified Cox models via inverse variance-weighted meta-analysis.

Results: The adjusted HR was 3.04 (95% CI: 2.81, 3.27) for ACEIs, 1.16 (1.00, 1.34) for ARBs, and 2.85 (1.34, 6.04) for aliskiren based on the Fireman approach. The corresponding HR was 2.98 (2.76, 3.21), 1.15 (1.00, 1.33), and 2.86 (1.35, 6.04) when using meta-analysis.

Conclusions: The case-centered logistic regression approach and meta-analysis produced similar effect estimates and confidence intervals, suggesting that both achieved similar level of confounding adjustment without the need to share individual-level data across multiple sites.

554. Adverse Reactions to Medicines Used in Cardiovascular Conditions in a Cardiac Care Unit

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Background: Cardiovascular drugs are the most common class of drugs associated with medication errors and adverse drug reactions (ADRs). However, available data pertaining to ADRs to cardiovascular drugs in the Indian population is very limited. There is need for studies to monitor the patients reciveing cardiovascular drugs for occurrence of ADRs.

Objectives: To assess the prevalence, severity, predictability, preventability and to identify the risk factors for development of ADRs to cardiovascular drugs.

Methods: Patients admitted to the cardiac care unit were enrolled in the study and followed on a daily basis for occurrence of ADRs. Causality of ADRs was assessed using WHO scale and Naranjo's algorithm and the reactions were coded according to WHO adverse reaction terminology. Seriousness of the ADRs was assessed as defined by ICH. The statistical analysis of data was done using Chi square test and Fisher exact test. Bivariate logistic regression was used to identify the risk factors.

Results: Total of 637 patient episodes from 613 patients (Male-68.6%) were followed. Prevalence of ADRs was found to be 36.7% (234). A major proportion of the patients experienced ADRs (95.29%) and were moderate in severity. One hundred and forty-six ADRs were predictable (62.3%), whereas 213 ADRs were not preventable (91%). The majority of the ADRs (38%) affected the metabolic system. Amongst the cardiovascular drugs, diuretics frequently caused ADRs (32.7%). Female gender (OR: 1.4 [CI: 1–1.9], $p < 0.0001$), elderly (>60 yr) (OR: 1.9 [CI: 1.3–2.7], $p < 0.04$), number of co morbid conditions (>2) (OR: 4.4[CI: 2.3–8.8] , $p < 0.0001$), length of hospital stay (>10 days) (OR: 9 [CI: 3.6–25.8], $p < 0.0001$), smoking ($p < 0.001$) and number of medications received >10 drugs) (OR: 2.1 [CI: 1.2–3.9], $p < 0.01$) were identified as predisposing factors for development of ADRs.

Conclusions: The prevalence of the ADRs was more when compared to other studies (36.73%). Elderly patients experienced majority of the ADRs (32.1%). In patients with concomitant diseases (>2) ADRs were common due to polypharmacy. Interventions to reduce the risk for development of ADRs in hospitalized cardiac patients should focus on the identified risk factors.

555. Non Steroidal Anti-Inflammatory Drugs (NSAIDS) and Increased Risk of Hypertension Treatment Intensification: A Population-Based Cohort Study

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Background: Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are known to antagonize the effects of antihypertensive drugs. Their associations can lead to an increase in arterial blood pressure. However, the impact of NSAIDs on hypertension treatment management in large-scale populations remains poorly evaluated.

Objectives: We evaluated if the introduction of NSAIDs could induce an intensification of hypertension treatment (defined as the introduction of a new antihypertensive drug).

Methods: We conducted a cohort study on 5,710 hypertensive subjects of the French Health Insurance System Database, treated and stabilized with their antihypertensive therapy and not exposed to any NSAID prescription between 1 April 2005 and 1 April 2006. The maximum follow-up duration was 4 years.

Results: Adjusted Hazard Ratios (HR) for hypertension treatment intensification were 1.34 (95% CI: 1.05–1.71) for NSAIDs in general (and 1.95 [95% CI: 1.13–3.36] for oxicams in particular). There were significant interactions between NSAIDs and Angiotensin Converting Enzyme Inhibitors (ACEIs, HR = 4.09, 95% CI: 2.02–8.27) or Angiotensin Receptor Blockers (ARBs, HR = 3.62, 95% CI: 1.80–7.31), but not with other antihypertensive drugs.

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Conclusions: Exposure to NSAIDs (and to oxicams particularly) leads to an intensification of hypertension treatment, especially in patients treated with ACEIs or ARBs. Renin Angiotensin System blockers should be avoided whenever NSAIDs are prescribed.

556. Calcium Channel Blocker (CCB) Treatments and Cancer Risk: Linking Danish National Health Care Databases

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Background: The primary aim of the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) is to develop, test and disseminate methodological standards for pharmacoepidemiological studies. There has been a substantial increase in the use of CCB in the last decade and some studies have shown an increased cancer risk associated with use of CCB. Conducting studies on the possible association between CCBs and cancer using existing databases is challenging. In Denmark, a governmental initiative has ensured amassment of national health care databases and registers during the spring of 2012 to better address public health issues; i.e., cancer (The National Cancer Plan).

Objectives: The objective of this study is to investigate the association between CCB and overall cancer, breast cancer in woman, prostate cancer and colon cancer. The secondary objective is to investigate the increased possibilities for analyses due to the assembling of the Danish databases.

Methods: The study population includes all Danish Citizens in the years 2000–2009. We will link the following registers: The Register of Medicinal Products, the National Civil Registration System, the National registration of patients, The National Health Insurance Service Registry (GP), The Cancer Register and The Cause of Death Register. The analysis will be conducted as a cohort study and we will use Cox regression analysis with time-dependent covariates. Length of treatment will be calculated as package size timed number of packages.

Results: Preliminary analyses show that there has been an overall increase in the use of CCB from 3.5% to 6.5% during the years 2000–2009. The increase in the use of CCB is greater in the older age groups (both genders). There has also been an increase in overall cancer from approximately 500 per 100,000 to 580 per 100,000 (women) and 570 per 100,000 to 675 per 100,000 (men).

Conclusions: Full analysis will be conducted to explore the association between CCB and cancer, and to provide valuable information on the advantages on the amassment of the Danish Health Care databases.

557. Severe Liver Injury (SLI) among Dronedarone, Amiodarone or Sotalol Initiators

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Background: FDA received reports of SLI including hepatic failure in dronedarone-treated patients. Drug-induced liver injury (DILI) is a small fraction of SLI.

Objectives: To compare SLI identified in dronedarone vs. amiodarone or sotalol initiators as a pilot surveillance evaluation.

Methods: New user cohorts of dronedarone, amiodarone and sotalol-treated Medicare (FDA-CMS SafeRx) patients ≥65 years from 7/1/2009 to 5/31/2011 who were free of dronedarone, amiodarone, or sotalol dispensings as well as SLI-related diagnoses in the year prior to initiation were followed to first occurrence of a censoring condition: (SLI, 365 days follow-up, initiation of another study drug, end of study drug, death, disenrollment, or 5/31/2011). An algorithm was developed identifying acute SLI requiring primary hospital discharge diagnosis of acute/subacute liver necrosis (570.xx) or hepatitis unspecified (e.g., toxic, noninfectious hepatitis) with no diagnosis of a common hepatitis of specific diagnosed etiology within 14 days coupled with ≥1 severity indicator: death, hepatic coma (572.2x), liver transplant (50.5x), liver allotransplantation orthotopic (CPT 47135), liver allotransplantation heterotopic (CPT 47136), hepatorenal syndrome (572.4) or hematemesis (578.0). Incidence rates (IR) of SLI in dronedarone or amiodarone were compared separately with the sotalol IR.

Results: Two cases were identified in 27,748 dronedarone, three in 100,980 amiodarone, and 0 in 28,039 sotalol initiators. The IR per 100,000 person-years were 20 (95% CI: 2, 73) for dronedarone; 9 (95% CI: 2, 27) for amiodarone; and 0 (95% CI: 0, 29) for sotalol. Five of the 5 identified SLI cases were found to be possible cases on review of patient profiles (JRS) with medical record review pending.

Conclusions: No statistically significant differences were observed in SLI IR among initiators of dronedarone vs.

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amiodarone or sotalol. Further work is necessary to refine these risk estimates, validate the SLI outcomes, and determine which SLI cases may actually represent DILI.

558. Near Real-Time Safety Surveillance of Dabigatran among VA Users

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Background: Dabigatran was approved by FDA for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Due to lack of sufficient safety data outside of a clinical trial setting, a pharmacovigilance system that monitors the safe and appropriate use of dabigatran is needed. The current project aimed at assessing potential GI bleeding in dabigatran and warfarin new user cohorts using near real-time data in the Department of Veterans Affairs (VA).

Objectives: To assess the incidence of GI bleeding requiring hospitalization or an outpatient clinic visit for new users of dabigatran and warfarin in the VA.

Methods: *Design*: Using VA's integrated database, an evaluation was conducted in new users of dabigatran and warfarin. *Setting*: VA Healthcare System. *Source Population*: VA patients initiated on dabigatran or warfarin (new user cohort) between 11/1/2010 and 9/30/2011. *Main Outcome Measure*: GI bleeding, defined as a hospitalization or an outpatient clinic visit with a primary diagnosis by ICD-9 code. *Statistical Analysis*: Differences were assessed by chi-square or t-test.

Results: The dabigatran and warfarin new user cohort consisted of 809 and 44,023 patients respectively. Patients newly started on dabigatran were older than those on warfarin (mean age 77 years vs. 68 years, $p < 0.0001$), were more likely to have had a prior diagnosis of atrial fibrillation (89% vs. 48%, $p < 0.0001$), but less likely to have had risk factors for GI bleeding (31% vs.34%, $p = 0.028$), which included previous GI diseases, or concomitant medications like chronic NSAIDS. GI bleeding occurred in 8 dabigatran patients (incidence rate was 46/1,000 patient years, 95% CI 23.2, 92.6) and 706 warfarin patients (incidence rate was 47.5/1,000 patient years, 95% CI 44.1, 51.2), with incidence rate ratio of 0.97 (95% CI 0.49, 1.96). Mean number of days to GI bleeding was 79 following index date for dabigatran patients, and 76 days for warfarin ($p = 0.883$).

Conclusions: In this assessment using near real-time data, the incidence rate of GI bleeding was similar for new users of dabigatran and warfarin. Pharmacovigilance models of this type, while not formal studies, can rapidly provide data about potential safety signals.

559. Impact of Comorbidities on Risk of Cardiovascular Hospitalization among Patients with and without Atrial Fibrillation

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Background: Cardiovascular hospitalization (CVH) has a significant impact on health-related quality of life, healthcare costs, and utilization. Patients (pts) with recurring atrial fibrillation (AF) requiring CVH are not well characterized.

Objectives: To quantify the impact of AF and major AF comorbidities on risk of CVH among AF pts.

Methods: This retrospective cohort study assessed an administrative claims database (Thomson Reuters' MarketScan) for newly diagnosed AF pts and demographically matched non-AF pts. Pts aged ≥40 years with >364 days in the database were identified by a qualifying AF diagnosis (≥2 outpatient diagnoses within 30 days of each other or ≥1 inpatient diagnosis) from 1/1/04 to 6/29/09. Rate estimates were calculated to quantify association between diagnosis of AF and CVH relative to non-AF pts.

Results: Of 210,524 pts were included (mean age 74.0 ± 12.5 years, 49% male, 68% Medicare). Compared with non-AF pts, AF pts were more likely prescribed beta blockers (44% vs. 22%), digoxin (15% vs. 2%), and anticoagulants (29% vs. 2%); had a higher severity of illness (Charlson Comorbidity Index score ≥4; 16.5% vs. 4.1%); and had higher comorbidity prevalence (odds ratio; 95% confidence interval) of myocardial infarction (13.1; 11.7–14.7), heart failure (HF; 9.2; 8.9–9.6), and pulmonary embolism (8.2; 7.2–9.5). Risk of new CV events and comorbidities at follow-up was significantly ($p < 0.0001$) higher in AF pts, most notably major bleeding, HF, valvular disease, and stroke. AF pts with baseline comorbidities related to $CHADS_2$ score ≥2 or CHA_2DS_2-VASc score ≥4 experienced ≥2.0-fold higher risks of overall CVH vs. AF patients with scores of 0. AF pts had 3.4-fold higher CVH risk vs. non-AF pts; 24.3% of AF pts experienced recurrent AF requiring CVH (incidence: 176/1,000 person-years).

Conclusions: AF pts have higher burden of baseline CV comorbidities that portend greater risk of CVH and new CV comorbidities following diagnosis compared to matched non-AF pts. These data indicate AF recurrence requiring hospitalization and overall hospitalizations 1 year following diagnosis is common.

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560. Statin Use and Cataract Surgery – A Nationwide Retrospective Cohort Study

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Background: Since a report of lenticular opacities in dogs treated with high dosages of statins, the debate on the relationship between statin therapy and cataract has not come to a conclusion.

Objectives: The aim of this study was to evaluate the association between statin therapy and risk of cataract surgery in an ethnic Chinese elderly population using time dependent analysis to minimize immortal time bias.

Methods: A retrospective cohort study using the Longitudinal Health Insurance Database 2005 (LHID2005) randomly sampled from the National Health Insurance Research Database (NHIRD), Taiwan was conducted. Totally, 50,165 adults aged between 65 years and 90 years in 1998 without records of statin therapy or diagnosis of cataract between July 1997 and December 1997 were included into the analysis. The first record of lens extraction within the follow-up period (1998–2009) was set as the study endpoint. A propensity score was derived using a logistic regression model to model receipt of statin therapy as a function of the baseline characteristics and potential confounders for every subject. We used the time-dependent Cox regression model to test the relative hazard of undergoing cataract surgery between statin users and non-users while use of statins was treated as a time-dependent variable with controlling for baseline age and individual propensity score.

Results: Among the 50,165 enrolled subjects, 17,670 subjects with an incident lens extraction were identified during a median follow-up of 10.7 years. The incidence of cataract surgery was 49.7/1,000 person-years in statin-using period compared with 38.5/1,000 person-years in statin-non-using period. The adjusted hazard ratio of cataract surgery was 1.20 (95% confidence interval, 1.14–1.27, $p < 0.001$) in statin users compared with statin non-users.

Conclusions: Long-term use of statins was associated with an increased risk of cataract surgery.

561. Influence of Time Dependent Covariates on Estimation of Risk of Acute Myocardial Infarction Comparing Sulfonylurea with Metformin in Type 2 Diabetes

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Background: Although analyses in pharmacoepidemiology studies typically do not adjust for time-dependent covariates under a time-independent exposure definition (fixed exposure), adjustment for them with fixed exposure may control confounding by some unmeasured factors at baseline.

Objectives: To evaluate the potential influence of lipid-lowering medication (LLM) use during follow-up on the association of sulfonylurea (SU) vs. metformin (MF) with acute myocardial infarction (AMI) in type 2 diabetes (T2DM).

Methods: We analyzed data from 136,833 T2DM patients aged 25–64 years newly initiating MF/SU between January 2003 and June 2010 from a large U.S. health claims database. First AMI was defined by principal hospital ICD-9 diagnosis codes. LLM use at baseline and during follow-up was identified by prescription records. We defined MF/SU cessation as when a prescription gap was $>1/3$ of the duration of supply of the most recent prescription. We matched SU use 1:1 to MF use based on the propensity score (PS) (5–1 digits greedy matching). Hazard ratios (HR) for main effects were estimated by Cox proportion hazard models with adjustment for time-updated LLM use during follow-up.

Results: The patients were followed an average 0.4 years. Prior to PS matching, MF users had more LLM use (46.0% vs. 39.3%) at baseline and in follow-up (39.8% vs. 33.8%) compared to SU users. After PS matching, MF users still had more LLM use during follow-up (36.1% vs. 33.8%). The HRs (95% CI) for AMI with SU compared to MF, with and without adjusting for LLM use in follow-up, were both identical: 1.9 (1.3, 2.9).

Conclusions: No change was observed in the effect of SU use on acute AMI when adjusted for LLM use during follow-up, possibly due to the short follow-up times and younger age range in our study population.

562. Patterns of Comorbidities and Procedures among Patients with Metastatic Melanoma within SEER/Medicare (USA)

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Background: The incidence of metastatic melanoma (mMel) has been increasing over recent decades and has remained fairly untreatable. Recently, two new treatments have been approved for certain types of mMel. Because of

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increasing survival with new treatments, there is increasing need to understand comorbid conditions for patients with mMelThe incidence of metastatic melanoma (mMel) has been increasing over recent decades and has remained fairly untreatable. Recently, two new treatments have been approved for certain types of mMel. Because of increasing survival with new treatments, there is increasing need to understand comorbid conditions for patients with mMel.

Objectives: To determine the most frequent comorbid conditions and medical procedures for patients with metastatic melanoma.

Methods: We identified a cohort of 521 patients with metastatic melanoma in the SEER cancer registries, who were not identified as cases by autopsy and who had linkage to Medicare records. In order to identify clinical meaningful groupings of events, we applied the Clinical Classifications Software for ICD-9-CM from H-CUP and estimated the fraction of subjects who experienced ≥1 event in a given category.

Results: Subjects experienced a number of comorbid diagnoses. The most common diagnoses were related to cardiovascular events, gastrointestinal disorders, infection, endocrine disorders, and respiratory diseases (98.7, 91.0, 87.1, 93.3, and 96.2%), respectively. There is a significant burden of mental illness (67.8%) driven mainly by depression and mood disorders. Other than diagnostic procedures, the most commonly reported procedures were related related to management of metastatic disease (e.g., diagnostic procedures, including biopsy, and surgical procedures).

Conclusions: In the Medicare-eligible metastatic melanoma population there is a significant burden of disease involving multiple organ systems. As survival improves with new treatments, it will be important to recognize these risks when addressing the risks and benefits of new treatments.

563. Arterial Thromboembolic Events among Older Renal Cell Cancer Patients

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Background: The association between cancer and venous thromboembolic events (VTEs) is well established; however, the association between cancer and arterial thromboembolic events (ATEs) is poorly described. It is important to understand the scope of ATE risk, before and after diagnosis, in order to offer cancer patients optimal care and improved quality of life.

Objectives: The main goal of this study was to estimate and describe the incidence of ATEs before and after renal cell cancer (RCC) diagnosis.

Methods: SEER-Medicare linked data (1991–2003) was utilized for this retrospective cohort analysis of RCC patients. This database combines two large, population-based, geographically diverse U.S. data sources, providing detailed information about elderly persons (≥65 years).

Results: We observed that among older RCC patients, 4.8% experienced a transient ischemic attack (TIA), 9.9% experienced an ischemic stroke (IS), 5.9% experienced a MI, and 6.2% experienced unstable angina (UA) in the 12 months after RCC diagnosis. Compared to an age-matched non-cancer cohort followed during the same timeframe, RCC patients were 1.3–2.1 times more likely to have an ATE in the 12 months after RCC diagnosis. Regardless of subtype, over half of ATEs occurred in the first 90 days after RCC diagnosis. The strongest predictors of an ATE event in the 12 months after RCC diagnosis were recent history of that particular ATE, atherosclerosis, and kidney disease. RCC patients with a recent history of a CVD event (MI, UA, TIA, IS, or onset congestive heart failure) were 2.1–2.8 times more likely to have an ATE in the 12 months after diagnosis compared to those without a CVD history. RCC patients with a recent history of the ATE of interest were at even higher subsequent risk of that particular ATE after diagnosis (HR = 4.3–5.7).

Conclusions: Our results indicate that older RCC patients are at increased risk of ATEs after cancer diagnosis. ATEs are common and serious co-morbidities that should be closely monitored in older RCC patients, particularly during the first 3 months after diagnosis and among those with a recent history of an ATE.

564. Risk of Gastrointestinal Conditions among Patients with Atrial Fibrillation

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Background: There are limited data suggesting that gastrointestinal (GI) conditions are common in patients with atrial fibrillation (AF). However, many agents utilized by patients with AF are known to increase the risk of GI events.

Objectives: To describe the risk of GI events among patients with AF.

Methods: An analysis of insurance healthcare claims from the MarketScan® database (2005–2009) was conducted. All subjects aged ≥18 years as of the date of first AF diagnosis, with ≥180 days of continuous insurance coverage

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prior to the index AF and no GI event within 180 days of the index AF were selected. GI events were identified from claims with a primary or secondary diagnosis code for any GI condition and for the subset of GI conditions consistent with dyspepsia (upper abdominal pain, abdominal pain, abdominal discomfort and dyspepsia). The risk of GI events was assessed with incidence rates (IRs) (new GI cases/patient-years of observation). Subgroup analyses were performed with respect to gender, age and CHADS2 score.

Results: A total of 413,168 patients with AF and no GI event in the 180-day baseline period were identified. The mean (median; SD) age of all patients with AF was 67.7 years (69; 15); 43% were female. During the mean follow-up of 563 days, IRs of any GI event and dyspepsia for patients with AF but no GI symptoms at baseline were 38.8 and 14.7 events per 100 patient-years. Corresponding IRs of any GI events for female and male were 43.6 and 35.5; for patients in the age groups below 65, 65–74, 75–84 and ≥85 years IRs were 32.3, 38.9, 44.6 and 52.7; for patients with CHADS2 score of 0, 1–2, 3–4 and 5–6 IRs were 30.3, 41.6, 56.9 and 74.5, respectively. At baseline, 257,357 patients (62%) had at least one medication dispensed which may cause GI tolerability issues.

Conclusions: In this large claims database, AF was associated with approximately a 40% risk of developing a GI event, predominantly dyspepsia. A rising trend in IR was observed with increasing age and CHADS2 score. Higher propensity for GI events and agents that selectively cause higher symptomatic GI rates may relate to poor medication adherence in AF patients.

565. Patients with Obstructive Pulmonary Disease Have an Increased Risk of ECG Documented Out-of-Hospital Cardiac Arrest

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Background: Signals exist that patients with obstructive lung disease (OPD) have an increased risk of out of hospital cardiac arrest (OHCA), but evidence is scarce.

Objectives: 1. To determine whether patients with OPD have an increased risk of OHCA.

2. To identify subgroups with a high risk of cardiac arrest.

Methods: A prospective case–control study was performed, with 1,372 cases suffering from OHCA and 6068 age, gender, and OHCA-date matched controls. To ensure that OHCA resulted from cardiac causes, electrocardiogram (ECG) documentation of ventricular tachycardia/fibrillation (the most common causes of cardiac arrest) was required. Patients were considered to have OPD if they had at least 2 prescriptions of any medication with ATC code R03 within 1 year prior to OHCA date. Conditional logistic regression analysis was used to examine the risk for cardiac arrest in relation to OPD. Stratified analysis were performed regarding age category, gender, cardiovascular comorbidity, and disease severity (number of different respiratory drugs used within 6 months before OHCA date).

Results: Patients with OPD had an increased risk of OHCA compared to patients without OPD (adjusted (adj.) OR 1.4 [1.2–1.6], $p < 0.001$). The risk of OHCA was higher among females (adj. OR 1.8 [1.3–2.6], $p = 0.001$) than males (adj. OR 1.2 [1.0–1.5], $p = 0.032$). The risk of OHCA was comparable in the different age categories. Patients with more severe OPD (>3 respiratory drugs) had a higher risk of OHCA (adj. OR 1.8,(1.2–2.8), $p = 0.004$) than patients with moderate disease (three drugs, adj. OR 1.3 (0.9–1.8), $p = 0.150$) or mild disease (1–2 drugs, adj. OR 1.4 (1.1–1.7), $p = 0.007$). OPD patients with cardiovascular disease (adj. OR 3.7 [3.0–4.5], $p < 0.001$) had a higher risk of OHCA than OPD patients without cardiovascular disease (adj. OR 1.2 [0.9–1.7], $p = 0.299$) or patients without OPD, but with cardiovascular disease (adj. OR 2.6 [2.2–3.0], $p < 0.001$).

Conclusions: Patients with OPD have an increased risk of OHCA compared to patients without OPD. Of the patients with obstructive lung disease, women, patients with severe disease and patients with concomitant cardiovascular disease have the highest risk.

566. Awareness of Severe Hypertriglyceridemia in U.S. Adults: NHANES 2001–2008

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Background: Individuals with severe hypertriglyceridemia (SHTG; ≥500 mg/dL) have a substantially higher risk of developing coronary heart disease (CHD) and acute pancreatitis than individuals with lower TG levels. Cholesterol screening is an effective method for identifying individuals with elevated triglyceride (TG) levels who would benefit from behavior modification or drug therapy.

Objectives: To identify the proportion of American adults who reported having their cholesterol checked, to evaluate the characteristics associated with having cholesterol checked, and to assess the factors that are associated with cholesterol awareness among individuals with SHTG.

Methods: The sample included 7,988 of the adults (≥20 years of age) who participated in the National

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Health and Nutrition Examination Surveys (NHANES) 2001–2008. Polytomous logistic regression models were used to identify factors that were associated with time since the last cholesterol screening, categorized as screening < 2 years ago or 2 or more years ago

Results: Approximately 71% of US adults reported ever having their cholesterol checked. Only 56% of individuals with SHTG were aware of their condition. Factors significantly associated with awareness among those with SHTG included obesity, education, having insurance, having diabetes, and having a history of cardiovascular events.

Conclusions: The majority of adults in America have had their cholesterol checked; however, less than half are checking it annually. Furthermore, only half of those with SHTG were aware of having high cholesterol. Awareness is the first step in implementing strategies to attenuate the health risks associated with dyslipidemia.

567. Challenges in Evaluating External Validity of Predictive Models for Survival in Patients with Pulmonary Arterial Hypertension

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Background: Pulmonary arterial hypertension (PAH) is a rare, severe and potentially fatal disease. Predicting survival for PAH patients is critical for patient management. New predictive models for survival have been developed from large contemporary observational and prospective PAH registries in France and the United States

Objectives: To present epidemiological challenges associated with developing a study to evaluate the external validity of two predictive models for survival in patients with PAH.

Methods: Inter-study validation consisted of (1) evaluation of the French predictive equation in a validation cohort from the US registry; and (2) evaluation of the US prognostic risk score in a validation cohort from the French registry. Validation cohorts were built to approximate the inclusion/exclusion criteria originally defined by each registry to develop their predictive models.

Results: Our results focus on resolving the challenges in defining the validation cohorts. The two registries are conducted independently with different data fields and timepoints. Patient values are not available for all variables included in the predictive models requiring specific procedures for handling of missing data. In observational studies, randomization dates and discontinuation of study drug cannot be used to define the beginning and end of at-risk period. Thus, differences in registry design influence our ability to identify comparable definitions of time at risk for survival analyses. Narrowly defining the validation cohorts similarly to the original cohorts may limit the breadth of the external validity. However, it allows for a more precise statement about the generalizability as it pertains to applying US formulas in France and vice versa.

Conclusions: This study is a first step in the external validation of new predictive models for survival in patients with PAH. Collaboratively developing the research protocol has reduced the chances for unintended errors without adding the biases common to internal validation. Harmonizing collected variables in the future could obviate some of these post hoc challenges.

568. The Epidemiological Case–Control Results from the Drug-Induced Arrhythmia Risk Evaluation (DARE) Study

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Background: The aim of the DARE study was to establish a cohort of cases of drug-induced arrhythmic events reported throughout England in order to improve the understanding of drug- induced arrhythmia as a public health issue.

Objectives: Combining the epidemiological data with the collection of genetic data, the overall objective was to improve our abilities to predict those individuals who are at risk to help towards safer prescribing practice as well as to generate a unique population for future investigation and observation.

Methods: Cases of suspected drug-induced arrhythmia were referred from cardiologists in England from 2003 to 2011. Population-based controls were obtained from the general practitioners of the case patients. Predictive factors of drug-induced arrhythmia in this case control study were sought using multivariable logistic regression.

Results: 130 cases (mean age at interview 62.0 years SD 14.8, 62% female. Three hundred three controls were also recruited.(mean age at interview 67.0 years SD 11.5, 53.8% female). Multivariable logistic regression was performed for all cases and controls in the data. A parsimonious model of the risk factors was selected from stepwise regression with backward elimination using a significance level of 5%. The pseudo R^2 for the model was 0.49, the discrimination measure of the AUC was 0.92 (95% CI 0.89 to 0.95) and the Hosmer-Lemeshow test with 10 groups had a p-value of 0.546. These measures suggested that model fit was satisfactory. Risk factors were identified as hypokalaemia (odds ratio of 50.40 [95% CI 5.25–483.63]), hypothyroidism (OR 3.34, CI 1.09–10.21), previ-

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ous MI (OR 16.18, CI 4.21–62.21), previous heart valve problem (OR 4.37, CI 1.33–14.32) and previous heart rhythm problem (OR 25.38, CI 11.29–57.05).

Conclusions: Pharmacoepidemiologic research such as the DARE study can contribute to pharmacogentics by explaining the observed variability in adverse drug response in "real life" patients with polymorphisms in their genetic profile. Clinically caution in prescribing class 1 and III anti arrhythmic drugs alone or in combination with concomitant medications and co-morbidities can be advised.

569. Detection of QT Prolongation Signals Using an Electronic Health Record Database

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Background: Drug-induced QT prolongation can cause life-threatening arrhythmia. However, postmarketing surveillance based on spontaneous reporting systems has a limited ability to detect QT prolongation signal due to the rare incidence and reports. We hypothesized that a surveillance system based on electronic health records (EHRs) could be used to detect the signal because EHRs collect most of the clinical events in a hospital.

Objectives: To develop a QT prolongation signal surveillance system using EHR data.

Methods: We developed a QT prolongation surveillance system linked to the EHR database of a Korean tertiary teaching hospital. The database contains 15 years of ECG, clinical, and prescription data. The system performed a predefined case-crossover study. From the database, we selected 6,326 subjects (age 20–59 years) who had incident QT prolongation. For each subject, one case and one control period were matched. The drug prescribed in the 24-hour case period just before the event was compared with the drug in an earlier 24-hour control period, separated by a 72-hour washout period. Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence intervals (CIs), after adjusting for hospitalization and concomitant drugs known to be related to QT prolongation. A lower margin of the 95% CI >2 was considered a positive signal. To evaluate the system performance, 20 drugs were selected: 13 known to cause QT prolongation and seven others. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The time required for analysis was also checked.

Results: The sensitivity, specificity, PPV, and NPV of the system were 92.3, 71.4, 85.7, and 83.3%, respectively. On average, only 54 minutes were required to analyze one drug.

Conclusions: The developed system was fully automated and successfully detected QT prolongation signals with good performance and short analysis time using the linked EHR data. The system should be useful for surveillance of QT prolongation caused by marketed drugs.

570. ARITMO Project. QT Prolongation Associated to Antimicrobials, Antipsychotics and Antihistamines: An Analysis of the French Spontaneous Reporting Database

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Background: The ARITMO project aims to analyse the Torsade de pointes (TdP) and QT prolongation (QTP) potential of antipsychotics, antimicrobials and antihistamines. As part of this project, French pharmacovigilance data were analysed.

Objectives: To identify signals associating QTP events to the ARITMO project drugs of interest.

Methods: Reports collected in the French Pharmacovigilance database (January 2000–August 2010) were analysed. Adverse reactions were coded according to MedDRA, drugs according to ATC. Cases of TdP were identified thrugh MedDRA preferred term and database free text. Using the case-non case analysis, statistical signals for TdP were searched for all drugs belonging to the following classes: antipsychotics (N05A), antibacterials (J01, J04), antimycotics (J02), antiprotozoals (P01), antivirals (J05) and antihistamines (R06). A potential signal was defined as an association between the event and one of the studied drugs with 3 cases and a Reporting Odds Ratio (ROR) with 95% Confidence Interval Lower Limit exceeding one. Signals were defined as potential signals associating QTP with one ARITMO drug not mentioned in the Arizona CERT list, which include the drugs increasing the risk of TdP or QTP.

Results: In the subset of the French Pharmacovigilance database used 313 QTP cases were found, 145 (46.3%) of which were related to ARITMO drugs. Among these, antipsychotics (82 cases), antiprotozoals (25), and antibacterials (19) were the most represented drugs. The case non-case analysis identified 18 potential signals, nine of which concerned ARITMO drugs not included in the Arizona CERT lists. Of these, seven signals were found among antipsychotics and concerned amisulpride (13 cases), aripirazole (4), cyamemazine (27), levomepromazine (5), loxapine (5), olanzapine (7), and zuclopentixol

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(6). The other ones concerned alimemazine (7), and loratadine (3).

Conclusions: This study found signals of QTP for nine drugs. Another study showed similar results for TdP, indicating a consistence through signals having similar pharmacological background. These signals will be further evaluated taking into account concomitant drugs.

571. Giant Cell Arteritis and Cardiovascular Events in the French APOGEE Cohort. A Population-Based Study Using the French Health Insurance System Database

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Background: The risk of cardiovascular events (CVE) during giant cell arteritis (GCA) has rarely been quantified in population-based studies.

Objectives: To quantify the risk of CVE during GCA in a population-based GCA cohort and to compare it to controls using the French Health Insurance system database (FHISD).

Methods: The APOGEE cohort includes most incident GCA patients of the Midi-Pyrénées County, France from 2005 to 2008. GCA patients are identified in the FHISD by their ICD code (GCA with or without polymyalgia rheumatica). Incident cases are defined by a continuous glucocorticosteroids (GCs) course lasting for at least 6 months, and no previous exposure to GCs during the six preceding months. For each case two controls matched on gender and age were randomly selected. The cardiovascular risk factors (CVRF) were identified through the exposure to drugs prescribed to treat diabetes mellitus, hypertension or dyslipidaemia. CVE were cerebrovascular disease, coronary disease, peripheral arterial disease, congestive heart failure and atrial fibrillation. New CVE were identified by analysing comprehensive data on drugs' reimbursement, diagnostic procedures, hospital stays and new cardiovascular diseases registered in the database. Serious CVE were defined as CVE leading to hospitalization > 24 hours or death. Follow-up ended in April 2011. We compared the occurrence of the first CVE in cases and controls by a log-rank test.

Results: The cohort included 103 patients (80 women [77.7%];mean age 74.8 [± 9] years; mean follow-up 48.9 [± 14.8] months). The mean initial GC dosage was 54 (± 27) mg/day. At study entry, there was no difference between cases and controls for CVRF. CVE all combined as well as serious CVE occurred more frequently in GCA patients (respectively, 33% vs. 19%, RR = 1.8 [1.25–2.53], p = 0.0011 and 15.5% vs. 7.8%, RR = 2.0 [1.15–3.49], p = 0.014). The mortality rate among GCA patients was not different from matched-controls (8/103 vs. 18/206, $p > 0.05$).

Conclusions: In the general population, the probabilities of first non-serious and serious CVE are significantly increased among incident GCA patients.

572. What Is the Burden of Hospitalizations for Heart Failure in France in 2010?

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Background: Chronic heart failure (HF), common to multiple disease areas (coronary artery disease, hypertension, diabetes, atrial fibrillation…), has a high medical unmet need (due to its morbi-mortality) and high economic burden. Despite its severity, there is a lack of data on this disease in France, and particularly on the burden linked to HF-related hospitalizations.

Objectives: Our objective was to assess the number of hospitalizations related to HF in France over one year and to estimate its burden.

Methods: Data were extracted from the French national hospital database (PMSI MCO database) covering 96% of all hospitalizations in France. For this study, all hospitalizations with an ICD-10 code related to HF as principal diagnosis for 2010 were included. Over this one-year period, we looked at the number of hospitalizations, the related number of patients, the duration of hospital stay, and patients' age and outcomes.

Results: In 2010, there had been 210,490 hospitalizations in France with a code related to HF as principal diagnosis. Of 9.1% of them were hospitalizations of < 2 days. A hospital stay for HF had an average duration of 9.6 days (10.5 after exclusion of hospital stay shorter than 2 days). This number of hospitalizations was linked to 160,092 patients (mean age: 79.0 years), corresponding to a number per patient of hospitalizations of 1.3 and of days spent in the hospital of 12.7 (13.4 after exclusion of hospital stay shorter than 2 days). For 17.5% of the hospitalizations, patients spent on average 4.2 days in an intensive care unit. Of 92.2% of the patients came to hospital directly from home (via emergency rooms for 58.2% of them). Hospitalization mortality rate was 7.5%; 71.5% of the patients went back home directly after their hospitalization, and 20.6% were discharged to skilled nursing facilities.

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Conclusions: In applying the 2009 average cost for hospitalization due to HF (4,455€), the annual cost associated with HF-related hospitalizations in France is close to €1 billion. Any intervention that would significantly reduce HF-related hospitalization rate will consequently have a major impact on costs related to this disease.

573. Combining Electronic Health Records and Patient-Reported Information in the UK: Preliminary Results from WASPS (Wales SAIL + PRO Study)

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Background: As demand for real-world data increases, the need to adopt more time and cost-efficient research methods will grow. Direct-to-patient studies (patient recruitment without physician sites) are a novel, efficient approach to capturing PRO and electronic health record (EHR) data gaining proof in the US and the UK.

Objectives: The objective of this study was to deploy a direct-to-patient observational study in the UK that combined PRO and EHR data.

Methods: In October/November 2011, UK MediGuard.org members were invited to participate via email; enrollment was supplemented with digital outreach. Interested individuals accessed study information and screened based on a self-reported cholesterol problem. Participants completed an on-line survey and provided identifiers to be used only for data linkage. The system's NHS Trusted Third Party converted Study ID's into pseudo-identifiers to link PRO and SAIL data. The primary study endpoint was records matched based on patient identifiers and the secondary endpoint was validity of self-reported diagnosis.

Results: Two hundred and forty cholesterol patients in Wales enrolled within 6 weeks: 98 from uk.MediGuard.org and 142 from other digital channels. NHS Wales matched 226 of 240 (94%) to a pseudo-identifier (69 exactly, 157 with probability > 0.9). Ninty-one of 226 (41%) had at least one primary care record in SAIL and nearly all records (89 of 91, 98%) contained data suggesting a cholesterol problem. Matching cholesterol test dates ($\pm$6months) were located for 66 of 89 records (74%, Spearman correlation = 0.786, $p < 0.0001$) and there was a high positive correlation of total cholesterol values amongst the 1/3 of patients able to self-report data ($n = 28$, Pearson correlation = 0.785, $p < 0.0001$). Investigations of how to improve record availability are underway.

Conclusions: This study demonstrates the feasibility of linking PRO and HER data in SAIL, thus offering new research possibilities. Welsh individuals will participate in observational research, are willing to provide identifiers for EHR linkage, and provide truthful feedback about their condition.

574. Cardiovascular Risk Factors among Women in the United States by Race/Ethnicity

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Background: Current knowledge of cardiovascular risk factors among women in the United States is incomplete.

Objectives: To examine current national estimates for hypertension, high cholesterol, diabetes and obesity among women in the United States by race/ethnicity.

Methods: Cross-sectional observational study design. Analysis of nationally representative data collected from women participating in the National Health and Nutrition Examination Survey (NHANES) 2007–2008 (total women aged 20 years and older, $n = 3025$; non-Hispanic white, $n = 1366$; non-Hispanic black, $n = 639$; Hispanic, $n = 902$; other races, $n = 118$).

Results: More than a quarter of US women have hypertension (31.1%). Black women have a significantly higher rate of hypertension (45.0%, $p = 0.0003$) than whites (30.1%) and Hispanic women a significantly lower rate (26.4%, $p < 0.0001$). Of 29.3% of women of other races have hypertension. Hypertension affects four out of five black (82.5%, $p < 0.0001$) women and women of other races (82.1%, $p = 0.0091$) aged 65 years and older, but only three out of five white (60.6%) and Hispanic (63.5%) women of the same age. Of 8.7% of US women have diabetes. Black women are more than twice as likely as whites to have diabetes (17.2% vs. 7.0%, $p = 0.0019$), followed by women of other races (11.5%), and Hispanic women (11.4%). More than a third of US women have high cholesterol (38.5%). Prevalence rates are similar across race/ethnicity. Women of other races have the highest rate (41.7%), followed by whites (39.2%), blacks (37.0%), and Hispanics (35.5%).Obesity is prevalent in 35% of US women. Nearly half of black women are obese (48.9%) compared to less than a third of white women (32.7%, $p < 0.0001$). Hispanic women are more than twice as likely to be obese as women of other races (42.4% vs. 19.8%).

Conclusions: Prevalence rates of hypertension, diabetes and obesity are higher among black women, while women of other races are the most likely to have high cholesterol. Hypertension is particularly problematic for black and other women aged 65 years and older. Effective approaches are needed to reduce cardiovascular risk among these two groups of women.

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575. Persistence with Statins and Reduction of Low Density Lipoprotein Cholesterol: Analysis of Real-Life Data from Community Settings

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Background: The efficacy of statins in decreasing the cholesterol level in high-risk patients is well established. However, compliance with statins is relatively low and about half of patients discontinue therapy within several months.

Objectives: To quantify the association between persistence with statins and low density lipoprotein cholesterol (LDL-C) levels using "real-life" data in community settings.

Methods: A retrospective population-based cohort study was conducted among eligible 87,219 primary-prevention and 15,139 secondary-prevention patients who are members of a large health maintenance organization and initiated statins therapy between 1998 and 2008. Baseline and follow-up LDL levels were collected from three months prior to the date of first dispensed statins (index date) to 6 months afterwards. Persistence was assessed by proportion of follow-up days covered (PDC) with statins.

Results: Over the study follow-up period, there were significant ($p < 0.001$) reductions in LDL-C levels of 54, 33 and 13 mg/dL among highly persistent (PDC ≥ 80%), poorly persistent (33% < PDC < 80%), and non-persistent statins users (PDC ≤ 33%), respectively. In a multivariable model, high persistence with statins therapy was associated with a 27% and 25% decrement in LDL-C level among primary and secondary prevention cohorts, respectively. Similarly, a higher proportion of the persistent statins users reached target LDL-C level within the study follow-up period (80% and 58% among primary and secondary prevention cohorts), compared to only 28% and 17%, among non-persistent patients.

Conclusions: PDC with statins is strongly associated with LDL-C reduction, supporting the validity of using PDC methods as a measure of drug exposure.

576. Comparative Safety of Statins in Japanese Patients: A Short-Term Prospective Case-Cohort Study (Japan Statin Study, JSS)

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Background: Statin causes rhabdomyolysis, elevations of aminotransferases (AST/ALT) proteinuria (PU), hematuria (HU) and elevation of serum creatinine (SCre).

Objectives: To compare the incidence of rhabdomyolysis, CK (>10ULN), AST/ALT (>3ULN), HU (≥+), PU (≥++) and SCre elevation (>1.5 mg/dL) between different statins in Japanese patients.

Methods: Using case-cohort design, we assessed the association between events (rhabdomyolysis, CK, AST, ALT, HU, PU and SCre) and statins. Statin new users (including "switchers" from a different antihyperlipidemic agent) were defined as those who did not use the statin during the 6-month period prior to its first prescription and identified in 68 hospitals between January 2008 and July 2010. Subcohort (about 5% of registered patients) was sampled from new users. Only potential cases and subcohort were examined by the questionnaires for the detailed information and all potential cases were reviewed by three specialists. Hazard ratio (HR) adjusted for age, sex, concurrent diseases/drugs was estimated by the Cox proportional regression model with robust variance.

Results: A total of 6,877 statin new users were identified (median age: 66 years; males: 52%; "switchers": 25%). Rhabdomyolysis, CK, AST, ALT, HU, PU and SCre were developed in 1, 2, 11, 18, 78, 42 and 117 cases, respectively. Taking pravastatin as a reference, HR of AST/ALT was 2.3 [95% CI;0.1–38]/2.4 [0.3–17] for fluvastatin, 8.3 [0.9–79]/4.8 [1.0–23] for atorvastatin, 2.6 [0.3–28]/4.2 [0.9–20] for rosuvastain, and (no event)/0.5 [0.3–2.7] for pitavastatin, resepectively. HR of HU/PU was 0.2 [0.02–1.3]/1.0 [0.2–4.0] for fluvastatin, 1.0 [0.5–2.3]/0.7 [0.2–2.2] for atorvastatin, 1.8 [0.9–3.6]/1.8 [0.7–4.5] for rosuvastatin and 1.6 [0.7–3.5]/0.9 [0.3–2.7] for pitavastatin, respectively. HR of SCre was 3.9 [1.6–9.2] for fluvastatin, 2.2 [0.9–5.6] for atorvastatin, 2.3 [1.0–5.6] for rosuvastatin and 1.6 [0.6–4.2] for pitavastatin, respectively.

Conclusions: Compared with pravastatin, the incidence of AST/ALT and SCre tended to be higher with rosuvastatin, atorvastatin and fluvastatin. As the statistical power is not sufficient, further study is warranted.

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577. Glyburide Is Associated with an Increased Risk of Acute Coronary Events Compared to Gliclazide in Patients with a History of Ischemic Heart Disease

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Background: Sulfonylureas can block cardiac K_{ATP} channels and inhibit ischemic preconditioning, an endogenous protective mechanism in the heart provoked by prior ischemic events. At usual therapeutic doses glyburide is more likely to inhibit cardiac K_{ATP} channels than gliclazide. Patients with a history of ischemic heart disease (IHD) may be more likely to experience ischemic preconditioning.

Objectives: Therefore, we hypothesized these patients would be more susceptible to the adverse cardiovascular effects if they are using glyburide rather than gliclazide.

Methods: Using administrative health records from Alberta, Canada, we conducted a population-based nested case–control study among patients with a history of IHD and using either glyburide (n = 6,186) or gliclazide (n = 5,088) as their sole sulfonylurea between 1998 and 2008. Cases were defined as those with an acute coronary syndrome (ACS)-related hospitalization or mortality and matched with up to 4 controls on age, sex, and cohort entry year using risk-set sampling. Recent glyburide or gliclazide exposure was defined as a dispensation within 120 days of the case date within each risk set and four mutually exclusive exposure categories were created. Multivariable conditional logistic regression was used to estimate the adjusted odds ratio (AOR) for an ACS event.

Results: A total of 4,146 cases (males, 62.4%; mean age, 71.8 years; mean follow-up time, 2.4 years) and 16,462 controls were identified. Recent glyburide exposure occurred in 1,767 cases and 6,699 controls; whereas recent gliclazide exposure occurred in 1,255 cases and 5,131 controls. Recent glyburide exposure was associated with a higher risk of an ACS event compared to gliclazide (OR: 1.09; 95% CI (1.00–1.18). After controlling for baseline drug use and co-morbidities, recent glyburide exposure was still associated with a higher risk of an ACS event than recent gliclazide (AOR: 1.10; 95% CI 1.01–1.12).

Conclusions: Patients with a history of IHD are more likely to experience adverse cardiovascular events if they are using glyburide rather than gliclazide. Our observations support the hypothesis that the adverse cardiovascular effect of non-selective sulfonylureas is partially mediated by blockade of ischemic preconditioning.

578. The Use of Pioglitazone and the Risk of Bladder Cancer in Patients with Type 2 Diabetes

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Background: The safety of pioglitazone, an oral anti-diabetic agent in the thiazolidinedione class, with regard to bladder cancer risk is controversial.

Objectives: To determine if the use of pioglitazone is associated with an increased risk of incident bladder cancer in patients with type 2 diabetes.

Methods: Using population-based data from the United Kingdom General Practice Research Database, nested case–control analyses were conducted within a cohort of new users of oral hypoglycemic agents between January 1, 1988 and December 31, 2009. All incident cases of bladder cancer, occurring after one year of follow-up to account for latency, were identified and up to 20 controls were matched to each case on age, sex, year of cohort entry and duration of follow-up. Exposure was defined as ever use of pioglitazone, along with measures of duration and cumulative dose. Rate ratios (RRs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression.

Results: The cohort included 115,727 new users of oral hypoglycemic agents with 470 patients diagnosed with bladder cancer during follow-up (rate 89.4/100,000 person-years). The 376 cases of bladder cancer that were diagnosed beyond one year of follow-up were matched to 6,699 controls. Overall, ever use of pioglitazone was associated with an increased risk of bladder cancer (RR: 1.74, 95% CI: 1.04, 2.91). The risk increased as a function of duration of use, with the highest risk observed in patients exposed for >24 months (RR: 1.92, 95% CI: 1.10, 3.36), and a cumulative dose >28,000 mg (RR: 2.47, 95% CI: 1.02, 5.98).

Conclusions: The use of pioglitazone is associated with an increased risk of incident bladder cancer among patients with type 2 diabetes.

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579. The Burden of Type 2 Diabetes on Work Productivity: A Systematic Review

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Background: Type 2 diabetes is a common disease which may impact employees, employers, payers and society in terms of lost productivity at work.

Objectives: To describe the risk and magnitude of work productivity losses among individuals in the labour force with type 2 diabetes as compared to those without diabetes.

Methods: A systematic review was conducted through a literature search of published studies using Medline, Embase, Psych-Info, Proquest and the Occupational Health and Safety reference collection. Databases were searched from their start date until June 2011. No language restriction was applied. Studies were included if: (1) the effect of type 2 diabetes on absenteeism, presenteeism, productivity loss, unemployment/employment, disability or early retirement was measured; and (2) a cross-sectional, cohort or Case–Control design was used. Two authors independently selected studies, extracted data and assessed quality. Since there was substantial heterogeneity among studies, our synthesis is reported in the form of a descriptive analysis.

Results: Twenty-six studies were included. Type 2 diabetes was significantly associated with an increase in productivity loss or retirement in all of the nine studies focussing on these outcomes. A significant trend toward increased absenteeism, employment and disability was observed in 16 of the studies. No consistent data was available for presenteeism. The quality of studies was variable.

Conclusions: Type 2 diabetes seems to have a considerable impact on lost productivity at work. There is a need for interventions targeting workers as the burden of type 2 diabetes is likely to increase in the coming years.

580. Incidence of Diabetic Maculopathy among Patients with Diabetic Retinopathy

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Background: Diabetic maculopathy (DMP) is a microvascular complication of diabetes that can be responsible for significant visual loss in patients with diabetic retinopathy (DR).

Objectives: To estimate the incidence rate (IR) of DMP in a cohort of diabetic patients newly diagnosed with DR, overall and by diabetes subtype (type I and type II), in a UK population.

Methods: We conducted a cohort study using The Health Improvement Network (THIN) database in the UK. A cohort of subjects with a first-ever diagnosis code for DR between January 1st 2000 and December 31st 2008 and without a previous code for DMP, was followed from the day after first DR diagnosis (start date) to first diagnosis of DMP, age 85 years, death or 31 December 2008, whichever occurred first. IR was calculated dividing the total number of patients with DMP by the person-time contributed by all study cohort members.

Results: The study cohort consisted of 7,779 newly diagnosed DR patients, 30 of them were aged 6–15 years. Individuals who were diagnosed with DMP concurrently with retinopathy (n = 430; 2 of them aged 14 and 15 years) were excluded. Among the remaining 7,349 DR patients, we identified 318 individuals (1 aged 15 years) with a diagnosis code of DMP during a mean follow-up time of 2.4 years, resulting in an IR of 18.3 (95% CI:16.4–20.4) per 1,000 person-years. The mean time to develop DMP from DR was 1.7 (range: 5 days to 7.1 years) years, 1.6 years in diabetes type I and 1.7 years in diabetes type II. The IR was 25.7 (95% CI: 12.9–51.5; n = 8 cases) per 1,000 person-years in diabetes type I and 18.1 (95% CI: 16.2–20.3; n = 310 cases) per 1,000 person-years in diabetes type II.

Conclusions: In UK primary care, the incidence of DMP among diabetic patients affected with DR is high in both type I and II diabetes. Over half of DMP cases were diagnosed concurrently with the retinopathy, suggesting a delay in diagnosis of DR.

581. Risk Factors for Incident Diabetic Macular Edema in Type II Diabetes in UK Primary Care

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Background: Diabetic macular edema (DME) is a sight-threatening microangiopathy that can appear at early stages of retinopathy and is common in type II diabetic patients.

Objectives: To estimate the DME incidence rate (IR) and to identify risk factors for incident DME in type II diabetes in the context of current management of diabetes in UK primary care.

Methods: We conducted a Case–Control analysis nested in a cohort of newly diagnosed type II diabetic patients aged 1–84 years identified in The Health Improvement Network (THIN) database between 2000 and 2007. We followed patients until diagnosis of DME (N = 211),

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85 years of age, death, or 31st December 2008. DME diagnosis was confirmed by general practitioners in 86% of instances. Cases were all patients diagnosed with DME and controls were a random sample of study cohort members (N = 2,194). No matching was applied. Index date was the DME date for cases and a random date for controls. Adjusted odds ratios (OR;95% CI) were estimated for life-style factors, medical condition and hypoglycemic drugs.

Results: The IR of DME was 0.84 per 1,000 person-years (95% CI: 0.73–0.96). DME risk (OR; 95% CI) increased with glycated hemoglobin ≥7% (1.49;1.07–2.09), systolic BP ≥160 mmHg (2.22;1.31–3.76), proteinuria (1.94;1.37–2.74), LDL ≥3.0 mmol/L (1.75;1.16–2.64), total cholesterol ≥5 mmol/L (1.65; 1.15–2.37), and cataracts (4.03;2.69–6.03). DME risk was decreased among current (0.48;0.29–0.79) and former smokers (0.54;0.35–0.85), overweight (0.58;0.32–1.04) and obesity (0.57;0.33–0.98), and subjects with triglycerides/L ≥ 1.7 mmol (0.55;0.38–0.79). Diabetes duration, diastolic BP or HDL were not associated with DME. Use of sulphonylureas (2.97;2.10–4.20), insulin (2.82;1.67–4.75) and glitazones (1.82;1.13–2.93) were associated with an increased risk of DME.

Conclusions: We identified multiple factors associated with DME such as high glycated hemoglobin, systolic BP, total cholesterol, LDL, proteinuria, cataracts, and use of hypoglycemic drugs. The inverse association between smoking, obesity and triglycerides with risk of DME deserves further research.

582. Type 2 Diabetes Mellitus and Cancer Risk: A Population-Based Study

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Background: Recent epidemiological studies have suggested associations between type 2 diabetes (T2DM) and increased risks for various cancers.

Objectives: To estimate the incidences of seven major cancer types in T2DM vs. non-diabetic populations in the United Kingdom (UK).

Methods: We conducted a descriptive study using General Practice Research Database (GPRD), a UK population based electronic medical record database. Adults aged 18 years or older during years 2003–2010 were included. The seven cancer types were bladder, breast, colon, liver, lung, pancreas, and prostate. Incident cancer cases were defined as those with the first cancer diagnosis during the study period and at least 1 year prior continuous GPRD recording. T2DM status were determined by diagnosis and/or medication use. Crude and age-sex adjusted incidence rates for each cancer type were calculated in the overall GPRD population, the T2DM population, and the non-diabetic population, respectively.

Results: The cancer incidence rates in the overall GPRD population were comparable to those reported by UK Office for National Statistics. The incidence rates in the T2DM population were substantially higher than those in the non-diabetic population for all the seven cancer types. The differences reduced after standardized to the overall GPRD population by age and sex. The standardized incidence rates (95% confidence interval) per 100,000 person-year were 33.1 (19.4, 46.7) vs. 26.7 (21.5, 32.0) for bladder, 218.7 (217.4, 220.0) vs. 201.9 (201.6, 202.3) for breast, 55.4 (53.2, 57.6) vs. 39.6 (38.7, 40.4) for colon, 5.5 (5.1, 5.9) vs. 2.0 (1.8, 2.2) for liver, 71.8 (69.0, 74.5) vs. 58.4 (57.4, 59.5) for lung, 32.7 (31.8, 33.6) vs. 9.8 (9.3, 10.4) for pancreas, and 143.4 (136.2, 150.6) vs.168.9 (166.4, 171.3) for prostate.

Conclusions: The T2DM population in UK appears to have higher risks for multiple cancer types than the non-diabetic population. The increased cancer risks cannot be explained by age and gender difference. Further research is warranted to investigate whether the increased risk is due to T2DM, common risk factors, detection bias, or other factors.

583. Estimating Chronic Kidney Disease in a UK population with Type II Diabetes Mellitus

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Background: Major causes of mortality in type II diabetes mellitus patients (T2DM) are related to macro- and micro-vascular diseases. Chronic Kidney Disease (CKD) based on glomerular filtration rates (GFR), is associated with an increased risk of cardiovascular disease and mortality. The interaction between T2DM and CKD on CVD outcomes is not well understood, in part due to lack of consensus regarding the optimal measure for diabetic nephropathy in observational studies (Levey A S, *Ann Intern Med* 2009).

Objectives: The main objective of this study was to describe CKD in a T2DM population. The secondary objective was to compare the frequency of CKD when applying the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epi Equation (CKD-EPI) with the READ code classification of CKD.

Methods: The population studied includes men and women with a medical code for T2DM or anti-diabetic treatment codes during the study period (January 1, 1995 to December 31, 2010). The index date was defined as the first diagnosis or treatment in patients with at least one year of data prior to inclusion. READ codes were used to identify the population. The study was conducted in the General Practice Research Database (GPRD) comprising of medical records of general practitioners (GPs) in the UK with approximately 5 million patients. In eligible

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subjects, prevalence estimates 12 months prior to T2DM diagnosis and post-diagnosis incidence rates per 1,000 patient years (1,000 ptyrs) were calculated for CKD by stage. Estimates of person-time incidence rates are presented with confidence intervals at the 95th percentile.

Results: Among T2DM subjects (n = 268,618) the following CKD subpopulations were identified: MDRD-4 n = 10,095, CKD-Epi n = 12,405, and CKD Read codes n = 40,024. Incident cases of CKD, eGFR < 60 mL/min/1.73m^2 for all ages and sex were: MDRD-4 IR 5.71/1,000 ptyrs (5.60, 5.83); CKD-Epi IR 7.06/1,000 ptyrs (6.93, 7.18); and CKD Read codes IR 23.86/1,000 ptyrs (23.63, 24.09).

Conclusions: This study suggests that measures of eGFR estimate more similar CKD incidence rates while Read codes identified a much greater number of incident CKD cases in T2DM subjects from the GPRD. Additionally, all rates were more pronounced in women than men and increased monotonically with age.

584. Algorithm To Estimate Duration of Known Type 2 Diabetes in Electronic Healthcare Databases

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Background: Time since diagnosis of type 2 diabetes mellitus (T2DM), an important confounder/risk factor for most outcomes, is not typically available in large automated healthcare databases in the US.

Objectives: To create an algorithm to estimate diabetes duration to serve as a proxy for this important variable.

Methods: Patients ≥40 years old and newly diagnosed with T2DM between 1998 and April 2011 (N = 214,259) were identified in the General Practice Research Database (GPRD). Patients were considered newly diagnosed if they had a new recorded T2DM diagnosis after at least 1 year of continuous eligibility in GPRD. The cohort was split into a derivation dataset to build the predictive model and a prediction dataset to test model performance. Age, sex, and most recent T2DM treatment (1, 2, 3+ oral or an injectable medication), diabetes complications, and other comorbidities were included in the predictive model. The last recorded T2DM treatment occurred after 2008 in $>80\%$ of patients.

Results: In the derivation dataset, T2DM treatment was significantly associated with diabetes duration: ˜60% with 8 years had 3 + oral or an injectable medication vs. ˜30% with 2 years. Diabetic retinopathy (DR) was also significantly associated with diabetes duration; after 2 years the proportion of patients with DR increased 0.4-1.2% per year from a baseline of 5.2%. The prediction model estimated duration of disease within ± 1 year of observed duration 62.8% of the time, 70.5% within ± 2 year, and 77.5% within ± 3 year.

Conclusions: In the GPRD, time since diabetes diagnosis can be reasonably approximated using age at treatment, sex, T2DM treatment complexity, and diabetes complications. This supports the use of such an algorithm in healthcare databases without age at diagnosis to estimate duration of T2DM using data generally available in these databases.

585. Using Functional Principal Component Analysis (FPCA) for Sparse Longitudinal Data (SLD): Example of HbA1c in Patients with Diabetes Mellitus

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Background: Longitudinal observational studies often examine the change in continuous variables with time. Where measurements are sparse and irregularly spaced, a challenge emerges in how best to measure change over time.

Objectives: To predict the continuous trajectory of individuals with SLD by applying FPCA and to test the accuracy of the prediction.

Methods: All available data on HbA1c are collected from a population of 400 patients with diabetes sampled from the GPRD between 1/1/2009 and 30/06/2011. Using FPCA, the trajectory of each patient is estimated using patient-specific data with strength drawn from the whole population. The above procedure is repeated after randomly removing the last data point for 78/400 patients. Results are presented as the average squared error (ASE) for each individual using the complete and depleted datasets. The differences (d) between the true and predicted last HbA1c value are also estimated using the complete and depleted datasets, categorised as $d \leq -1$, $-1 < d \leq -0.5$, $-0.5 < d \leq 0$, $0 < d \leq 0.5$, $0.5 < d \leq 1$ and $d > 1$. Wilcoxon signed rank tests are used to test significance at the 5% level of significance. For benchmarking, a one unit HbA1c is associated with a 15% change in cardiovascular risk.

Results: The complete dataset consists of 2–10 HbA1c measurements (median 4) for each patient. The median ASEs of 0.069 and 0.066 for the complete and depleted datasets respectively are comparable. The differences in the predicted and original values of the last observation per individual using the complete/depleted datasets are very similar and categorised as follows:

$d \leq -1 = 10/11$
$-1 < d \leq -0.5 = 27/33$
$-0.5 < d \leq 0 = 192/188$
$0 < d \leq 0.5 = 123/125$
$0.5 < d \leq 1 = 38/29$
$d > 1 = 10/14$

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Between the two datasets, Wilcoxon rank sum tests did not suggest a statistically significant change in (1) the ASE values, with p-value = 0.16 or in (2) the differences between the predicted and true values for the last observations, with p-value = 0.07.

Conclusions: FPCA allows us to predict trajectories for SLD, thus facilitating estimation of change from baseline in longitudinal observational studies.

586. Combining Phase III and Phase IV Data: The Example of Rosiglitazone

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Background: Rosiglitazone was recently suspended from the European market due to increased risk of myocardial infarction (MI) while it remains on the US market under some restrictions. Extensive information is available from phase III randomized controlled trials (RCTs) and phase IV which includes both RCTs and observational studies.

Objectives: To propose a new method to estimate risk at an earlier stage use by combining available data from randomized controlled trials (RCTs) and observational studies on rosiglitazone by using Bayesian statistics.

Methods: We searched PubMed for randomized controlled trials (RCTs) and observational studies on rosiglitazone, among adult patients, published before March 8th 2011. All studies had to mention the endpoint myocardial infarction (MI) or have an adverse drug reaction (ADR) section where all ADRs were mentioned. Studies were weighed into our model based on their quality and relevance. A non informative posterior probability was used. Some of the studies included several rosiglitazone and/or comparison arms. First we compared all arms containing Rosiglitazone (per study) with all comparator arms (per study) combined. Accumulated data for each year on the market was added to the model estimating the relative risk (RR, 95% credible interval) of a MI after every year on the market. Secondly we compared the rosiglitazone arms (per study) to estimate the effect of co-medication. Included covariates: study weight, year of publication, type of study, size, duration and male/female ratio.

Results: In total 65 studies were included, 47 RCTs and 18 observational studies, published between 1999 and 2010. Study size ranged from 40 to 891,901 patients (average 32805.3). Average duration was 92.2 weeks. The final results from the yearly Bayesian risk estimates for MI will be presented at ICPE 2012.

Conclusions: Using Bayesian statistics makes it possible to make use of all available information to provide more intuitive results and a greater flexibility in modeling. This should aid the decision makers that have to make decisions based on both RCT and observational data.

587. Diabetes Mellitus, Antidiabetic Drugs and the Risk of Developing Rosacea

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Background: Rosacea is a chronic skin disease with a presumed key vascular component. Like rosacea, diabetes mellitus (DM) is associated with vascular dysfunction, with insulin as an important regulator of microvascular perfusion. We are not aware of any studies on rosacea in association with DM and use of antidiabetic drugs.

Objectives: To analyze the association between DM, use of antidiabetic drugs (insulin and oral antidiabetics [OADs]) and the risk of incident rosacea.

Methods: We conducted a matched (1:1) case–control analysis using the UK-based General Practice Research Database. We included cases with an incident rosacea diagnosis between 1995 and 2009, and compared the prevalence of DM and the exposure to insulin and OADs prior to the index date between cases and controls.

Results: We identified 60,042 rosacea patients and the same number of controls. DM was not associated with an altered risk of developing rosacea (odds ratio, OR 0.97, 95% CI 0.86–1.07), after adjusting for potential confounders. Insulin use in the absence of OADs showed a dose response relationship with a significantly decreased OR of 0.66 (95% CI 0.50–0.88) in current long-term users (40 + prescriptions/last prescription <180 days). Use of insulin with concomitant or previous use of OADs also revealed decreased ORs with the lowest OR of 0.67 (95% CI 0.51–0.87) for current insulin users with past OAD use. Use of OADs per se did not substantially alter the risk estimate. The null result was present in all strata after stratification by timing and duration of drug use as well as by various drug classes (e.g., biguanides, sulfonylurea, thiazolidinediones etc.).

Conclusions: Our study provides evidence for a lower rosacea risk associated with long-term insulin use, regardless of concomitant or previous OAD use. The effect might be restricted to late-stage diabetics; recent data suggest that insulin may increase microvascular perfusion and may balance vasoconstriction in the insulin sensitive state. In

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the insulin-resistant state, this property may be abolished, resulting in increased vasoconstriction upon insulin exposure. DM as a disease and OAD use did not alter the risk of incident rosacea.

588. Evaluation of Methods To Estimate Days' Supply of Oral Antidiabetic Drugs in the Health Improvement Network

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Background: Determination of days' supply in pharmacoepidemiology research is vital to determining exposure periods. However, the variables needed to calculate days' supply may be missing or incomplete within population-based data sources.

Objectives: To examine the ability of three methods to estimate days' supply for oral antidiabetic drugs (OADs) in The Health Improvement Network (THIN).

Methods: We conducted a retrospective cohort study among THIN patients 18 years of age or older who had: (1) at least three prescriptions for a newly initiated OAD between January 2008 and May 2011; (2) complete dosage instructions for all OAD prescriptions; and (3) at least 180 days of enrollment prior to the OAD prescription. The quantity of OAD prescribed divided by the number of prescribed dosage units per day (daily dosage) represented the gold standard for days' supply. Three methods to impute days' supply of OADs were evaluated: (1) imputed a 30-day supply for all prescriptions (Method 1); (2) imputed the median duration between consecutive prescriptions of OADs as the days' supply (Method 2); (3) imputed the mode daily dosage for a given OAD formulation and prescription quantity (Method 3) to calculate days' supply. The median (IQR, 10th to 90th) difference in days' supply between each imputed method and the gold standard was determined.

Results: Overall, 79,626 patients met the inclusion criteria, representing 2.6 million OAD prescriptions. There was a large difference in days' supply between the gold standard and Method 1 (median difference, -26 days; IQR -266 to 2 days; 10th to 90th -761 to 2 days) but little difference between the gold standard and Methods 2 (median difference, 0 days; IQR, -2 to 3 days; 10th to 90th -26 to 28 days) or 3 (median difference, 0 days; IQR, 0–0 days; 10th to 90th -267 to 0 days).

Conclusions: Imputation with a 30-days' supply for OADs may prematurely censor exposure follow-up time. Imputing the median duration between prescriptions or imputing a mode daily dosage based on the drug formulation and prescribed quantity, both closely approximated the gold standard for days' supply. Results might be different with different drugs or in different datasets.

589. Disinvestment Debate in a Brazilian State: Insulin vs. It's Analogue Glargine for Diabetes Control

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Background: Influenced by the growth of judicial demand and by the promise of better efficacy in terms of reducing the hypoglycemia episodes, in 2005 the glargine analogue was incorporated in the Minas Gerais State Public Health System (SUS) for type 1 diabetes mellitus. Currently around 2.7 thousand people are receiving the drug by the SUS free of charge. The expenses for State Government are approximately six million dollars year (2010). The crescent budget impact and recent studies about glargine and incidence of malignancies motivated managers to demand the Federal University of Minas Gerais for appraisal about efficacy and safety of the drug.

Objectives: To assess the efficacy and safety of the glargine analogue compared with another insulin's and to evaluate the pertinence of maintaining the drug on the list of the Public Health System (SUS) in the Minas Gerais State in Brazil.

Methods: Systematic Literature Review.

Results: Starting from 803 studies found in selected databases, only eight trials met the inclusion criteria for this review. Most of the trials were of poor methodological quality or had a high risk of bias with a mean score of 2.9 on the Jadad scale. The report of details the methodology was incomplete for most studies, either by lack or deficiency in the dissemination planning and implementation. No study could be classified as double-blind, and no results were identified that documented the increased efficacy of the glargine analogue in relation to glycaemic control and hypoglycaemic episodes simultaneously.

Conclusions: The present study demonstrated no benefit of therapy with glargine over other insulin formulations studied when analysed together the glycaemic control and the frequency and severity of hypoglycaemia. Besides the poor evidence the quality of the studies does not endorse the maintenance of the product in the public health system. We therefore recommend to the State Authority of SUS the disinvestment or the renegotiation to reduce the price of glargine.

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590. Socio-Demographic Characteristics and ADR Severity in Antidiabetic-Treated Patients: Profiles and Correlations

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Background: Population characteristics are known to be relevant on epidemiological studies of Diabetes Mellitus, but scarce information is published about the profile of antidiabetic-treated patients who suffer adverse drug reactions (ADRs), especially if severe.

Objectives: To analyze socio-demographic characteristics and ADR severity in antidiabetic-treated patients from spontaneous ADR reports.

Methods: Information from spontaneous ADR reports of antidiabetic-treated patients, including any treatment of A10A "Insulin and analogues" and/or A10B "Oral Hypoglycemic Agents", collected during the 2000–2008 period was obtained from the Spanish spontaneous ADRs reporting database (FEDRA). We analyze the socio-demographic variables of age, gender and autonomous region of origin; and the ADR variable of severity/non-severity defined by European Union criterion. Age group distribution follows the Spanish National Statistics methodology. We obtain time and regional evolutions for age, gender and ADR severity. Multiple correspondence analysis (MCA) is performed to analyze the data variance and the correlations among variables.

Results: A total of 1,253 ADR cases are reported, with the highest interanual increase between 2001 and 2002 (196%). Out of all cases, 32% of patients age 65–74 years -the most prevalent in 2000 and 2008-, 58% are women -however, men increase from 33% to 48%-, and 63% are non-severe ADR -but 45% are severe in 2008-. La Rioja is the region with the lowest rate of reports ($<1\%$) and Catalonia with the highest one (15%). MCA including gender, autonomous region of origin and ADR severity displays better outcome (81% of data variance explained) than considering age groups into the analysis (68%). Autonomous region of origin is the highest correlated variable to ADR severity. Gender is the variable with less relevance. ADR severity is mainly related with Catalonia, Madrid and Galicia. La Rioja and Murcia are related with ADR severity in men.

Conclusions: A profile of woman 65–74 years old who suffers a non-severe ADR is common. Autonomous region of origin is a socio-demographic variable correlated to ADR severity in antidiabetic-treated patients.

591. Use of Thiazolidinediones and Risk of Bladder Cancer: Disease or Drugs?

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Background: Pioglitazone, a drug for the treatment of type 2 diabetes mellitus has been associated with a small increased risk of bladder cancer in observational studies. As a result, the French Medicines Agency has suspended the use of pioglitazone in July 2011. Diabetes mellitus itself has also been associated with bladder cancer.

Objectives: Objective of this study was to evaluate the risk of bladder cancer in diabetic patients according to thiazolidinedione (TZD) treatment, in relation the severity of underlying disease.

Methods: We conducted a population-based cohort study (1996–2007) utilizing the Danish National Health Registers. Oral antidiabetic users (n = 179,056) were matched 1:3 by year of birth and sex to non-users. Cox proportional hazards models were used to estimate hazard ratios (HRs) of bladder cancer. Time-dependent adjustments were made for age, comorbidity, and drug use. Four different treatment stages were defined:

stage 1 was defined as current use of either a biguanide or a sulfonylureum, stage 2 as current use of a biguanide and a sulfonylureum at the same time, stage 3 was assigned to patients using TZDs and stage 4 to patients using insulin.

Results: Compared with non-diabetic controls, patients using antidiabetic medication experienced a 1.3-fold increased risk of bladder cancer (adjusted HR 1.3 [95% CI 1.2–1.4]). No major differences were observed between the different treatment stages. The risk of bladder cancer varied between 1.2 [95% CI 1.0–1.4] in stage 4 and 1.4 [95% CI 1.3–1.6] in stage 1. The risk of bladder cancer with TZD use (stage 3) was similar to the other groups (adjusted HR 1.3 [95% CI 0.6–2.7]).

Conclusions: The association between TZD use and bladder cancer is probably confounded by the severity of the underlying disease. Our results do not support that patients should discontinue taking TZDs because of an increased risk of bladder cancer.

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592. Metformin Does Not Alter the Risk of Lung Cancer: A Case–Control Analysis

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Background: Metformin use has been linked to a decreased cancer risk.

Objectives: We explored the association between use of metformin or other antidiabetic drugs and the risk of lung cancer in particular.

Methods: We assessed the association between metformin,and other antidiabetic drugs and lung cancer using a case–control analysis in the UK-based General Practice Research Database (GPRD). Cases were people with an incident diagnosis of lung cancer. Up to six controls per case were matched on age, sex, calendar time, general practice, and number of years of active history in the GPRD prior to the index date. The contribution of various potential confounders including tuberculosis, chronic obstructive pulmonary disease (COPD), diabetes mellitus, and co-morbid conditions to diabetes was evaluated in univariate models, and final results were adjusted for BMI and smoking.

Results: Long-term use (≥40 prescriptions) of metformin was not associated with an altered risk of lung cancer (adj. OR 1.19 [95% CI 0.96–1.48]). Overall, use of sulfonylureas was duration dependently linked to a marginally decreased risk of lung cancer (adj. OR 0.77 [95% CI 0.64–0.91]). This risk decrease was observed in men (adj. OR 0.71, 95% CI 0.57–0.88) but not in women (adj. OR 0.90, 95% CI 0.66–1.21) and this risk decrease was not statistically significant in an analysis restricted to diabetic patients only (adj. OR 0.88, 95% CI 0.72–1.07). Long-term use of insulin was associated with a slightly increased risk of lung cancer (adj. OR 1.33, 95% CI 1.04–1.71), however, no consistent trend across duration strata was observed.

Conclusions: Metformin did not decrease the risk of lung cancer.

593. Histamine-2 Receptor Antagonists and the Risk of Lung Cancer in Diabetic Patients – A Nationwide Study

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Background: In vitro and computational studies suggest that histamine-2 receptor blockers (H2RBs) have anti-tumorogenic effect. Whether they have clinically protective effect against lung cancer occurrence remains unclear.

Objectives: To examine the possible protective effect of H2RBs against lung cancer by using large health insurance database.

Methods: We conducted a case–control study nested within a diabetic cohort. A total of 640,173 type 2 diabetic patients were identified from the Taiwan National Health Insurance claims database during the period of 1 January 2000 to 31 December 2000. As of 31 December 2007, patients with incident squamous cell carcinoma (SCC) and adenocarcinoma were included as cases and up to four age- and sex-matched controls were selected by risk-set sampling. Logistic regression models were applied to estimate the association between statin and lung cancer incidence. A sensitivity analysis using external survey data was applied to validate the association after full adjustment for the effect of cigarette smoking.

Results: A total of 1,182 incident SCC and 2,345 adenocarcinoma cases were identified, and 13,108 matched controls were selected. After controlling for potential confounding variables, the adjusted OR associated with H2RBs use was 0.65 (95% CI: 0.44–0.95) for cumulative dosage ≥360 DDD and was 0.66 (95% CI: 0.45–0.95) for cumulative duration ≥1 years. When we stratified on type of lung cancer, the protective association of longer duration of H2RB use was more evident for lung adenocarcinoma with the adjusted OR of 0.67 (95% CI: 0.45–0.99). Significantly reduced risk of lung adenocarcinoma was found for cimetidine use ≥1 year with adjusted OR of 0.59 (95% CI: 0.35–0.99)

Conclusions: Long-term H2RBs use more than one year may reduce the risk of lung adenocarcinoma in diabetic patients.

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594. Regional Differences in Baseline Characteristics of Type 2 Diabetes Mellitus Patients from the "Effectiveness of Diabetes Control with Vildagliptin and Vildagliptin/mEtformin" (EDGE) Study

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Background: Vildagliptin (vilda), a DPP-4 inhibitor, has been shown in clinical trials to efficaciously reduce HbA1c with a low risk of weight gain and hypoglycemia when given as monotherapy or combined with the most commonly prescribed oral antidiabetic drugs (OADs). EDGE aimed to assess the effectiveness and safety of vilda or fixed-dose vilda/metformin relative to comparator OADs in type 2 diabetes mellitus (T2DM) patients under real-world conditions. We present data on baseline (BL) characteristics of T2DM patients from various geographic areas of the world who participated in EDGE.

Objectives: To describe BL data in the EDGE intent-to-treat (ITT) population overall and stratified by region (i.e., Europe [E], East Asia [EA], India [I], Latin America [LA], Middle East [ME]).

Methods: EDGE is a prospective cohort study run in 27 countries worldwide. T2DM patients inadequately controlled by OAD monotherapy were assigned into one of two cohorts based on newly initiated add-on OAD: (1) vildagliptin; (2) other OADs (metformin, sulfonylureas, thiazolidinediones, others; excluding other DPP-4 inhibitors, or GLP-1 mimetics).

Results: The study initially enrolled 45,868 patients, of which 43,791 were included in the ITT population (E: 22,073 [50.4%]; I: 10,692 [24.4%]; ME: 4779 [10.9%]; LA: 3846 [8.8%]; EA: 2401 [5.5%]). The overall mean age ± standard deviation was 57.8 ± 11.8 years, mean T2DM duration was 5.5 ± 5.2 year, mean body mass index [BMI] was 29.0 ± 5.1 kg/m^2, mean HbA1c was 8.2 ± 1.3%. Patients from E were older (62.3 ± 10.9 vs. I 51.8 ± 9.9 year), had a longer T2DM history (6.3 ± 5.6 vs. ME 4.2 ± 3.9 year), and had the highest BMI (30.3 ± 5.2 vs. EA 25.2 ± 3.4 kg/m^2). Marked HbA1c differences were seen at BL: Lowest HbA1c values (%) were seen in EA (7.7 ± 1.3) and E (7.9 ± 1.3), noticeably higher levels in LA (8.5 ± 1.7), ME (8.5 ± 1.3), and I (8.6 ± 1.1).

Conclusions: BL EDGE data show marked regional differences regarding age, T2DM duration, and BMI at the time of add-on dual OAD initiation and that the point at which physicians intensify treatment remarkably varies by region.

595. Drug Induced Hypoglycemia in Hospitalized Patients: Prevalence, Incidence Rate and Risk Factors

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Background: Hypoglycemia is very common in diabetes patients treated with anti-diabetic drugs. Iatrogenic hypoglycemia poses a major challenge in diabetes management.

Objectives: To evaluate prevalence, incidence rate and risk factors associated with iatrogenic hypoglycemia.

Methods: This prospective study analyzed 900 diabetes patients hospitalized in medicine and surgery wards of a teaching hospital between June 2010 and February 2011. Hypoglycemia was defined as Capillary Blood Glucose (CBG) < 70mg/dL. The observed hypoglycemic events were assessed for causality (Naranjo's algorithm and WHO ADR probability scale), severity (Modified Hartwig and Siegel scale), predictability (based on frequency of occurrence and history of exposure) and preventability (modified Schumock and Thorton). Bivariate analysis was used to determine the predictors for development of hypoglycemia.

Results: Hypoglycemia was observed in 20.77% of patients and the incidence rate was 23.15 episodes per 100 patient-days. Hypoglycemia lead to hospitalization in 6.45% of patients. Risk factors for the development of drug-induced hypoglycemia include advanced age {OR 1.62 (1.16–2.27) p = 0.005}, number of medications [6–9 {OR 2.17 (1.19–3.95) p = 0.010] and ≥10 {OR 2.75 (1.49–5.06) p < 0.001}], number of co-morbidities [1–2 {OR 1.51 (1.05–2.18) p = 0.029}, ≥5 {OR 2.90 (1.87–4.51) p < 0.000}], low body mass index {OR 2.47 (1.27–4.82) p = 0.010}, history of diabetes {OR 1.91 (1.13–3.25) p = 0.0210} and increased length of stay {OR 1.42 (1.02–1.98) p = 0.038}.

Conclusions: Hypoglycemia is a common complication of anti-diabetic drugs. Advanced age, number of medications and co-morbidities, low body mass index, history of diabetes and length of stay predict the development of hypoglycemia. Measures should be undertaken to decrease the frequency of hypoglycemia in high-risk patient population.

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596. Treatment Patterns and Persistence in Hypertensive Diabetes Patients Treated with Fixed or Unfixed Combinations of Angiotensin Receptor Blockers (ARB), Amplodipine (AML) and Hydrochlorothiazide (HCT)

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Background: Hypertension substantially increases the risk of adverse outcomes attributable to diabetes. Persistence is crucial for a successful blood pressure control.

Objectives: To evaluate treatment patterns and persistence in hypertensive patients (pts) with diabetes mellitus type 2 (T2D) receiving unfixed dose or fixed dose double combinations with ARB, AML and HCT in Germany.

Methods: This retrospective study analyzed prescription data collected by general practitioners, using a longitudinal database, the German IMS Disease Analyzer. The database was searched for pts with hypertension (ICD-10 code I10) and T2D (defined as ICD-10 E11 and/or treatment with oral anti-diabetics) initiated on ARB with AML or HCT within 11/08-10/09 with a follow-up of at least 12 months. Persistence was defined as proportion of pts who remained on their initially prescribed therapy for 1 year. Differences between mean persistence values (days) were calculated by using multiple regression analyses adjusted by age, gender, region, insurance and co-morbidity.

Results: Overall, 90,762 T2D pts with hypertension were eligible for analysis. Treatment with ARB was documented for 21,631 pts (24%). Four thousand nine hundred and sixty-seven pts were initiated on unfixed dose or fixed dose ARB combinations: 62% on fixed ARB/HCT, 13% on fixed ARB/AML, 8% on unfixed ARB + HCT, 17% on unfixed ARB + AML; about 53% received further antihypertensive drugs (FAD). Mean days (d) of persistence were higher in pts with fixed dose compared to unfixed dose combinations (ARB/HCT: 209.7 d vs. ARB + HCT: 152.0 d, $p < 0.0001$; ARB/HCT plus FAD: 240.6 d vs. ARB + HCT plus FAD: 200.5 d, $p < 0.0001$; ARB/AML: 215.6 d vs. ARB + AML: 170.5 d, $p = 0.0018$; ARB/AML plus FAD: 248.2 d vs. ARB + AML plus FAD: 229.2 d, $p = 0.0270$).

Conclusions: These real-life data suggest that in Germany the vast majority of hypertensive diabetes patients initiated on ARB double combinations with AML or HCT receives fixed dose combinations. This is associated with greater persistence. Overall, the level of persistence indicates room for improvement of hypertension management.

597. Pharmacological Treatment of Heart Failure in Primary Healthcare in Stockholm – High Adherence to Guidelines but Still Room for Improvement

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Background: Heart failure (HF) is a severe and common cardiac disorder in elderly people. Several studies have shown that treatment with Renin-Angiotensin–Aldosteron-System (RAAS)-inhibitors decrease morbidity, hospitalization rates and mortality. Despite strong evidence and guidelines, previous studies have shown that patients with HF are not treated optimally. Access to individual data from health care registers has led to unique opportunities to study drug treatment in large populations.

Objectives: To determine to what extent patients with the diagnosis of HF in primary healthcare (PHC) in Stockholm, Sweden were treated with RAAS-inhibitors. Secondly, we aimed at describing the population of patients from a demographic and an epidemiological point of view.

Methods: A retrospective cross-sectional study, on diagnoses and dispensed drugs, was performed on individual patient data from regional registers in the County of Stockholm (2.1 million inhabitants). The population of HF patients was defined as patients who were residents in Stockholm in December 2010, had two or more consultations with a recorded diagnosis of HF (ICD-10 code I50) during 2005–2010 and had been registered at least once for HF in PHC. Drug treatment was assessed as the proportion of the patients dispensed drugs, relevant in treatment of HF, between July and December 2010.

Results: A total of 13,571 patients (women 54%, men 46%) with diagnosis HF were identified. Sixty percent of them were treated with RAAS-inhibitors. Other relevant drugs used in treating the patients were as follows: betablockers 62%, loop diuretics 59%, spironolactone 17%, digitalis 12%, long-acting nitrates 13%, and thiazides 9%. The average age of the patients was 80 years (83 women vs. 78 men) and 95% were 60 years or older. The patients had the following comorbidities: 57% hypertension, 41% atrial fibrillation, 15% chronic obstructive pulmonary disease and 12% stroke/TIA.

Conclusions: A majority of all patients with HF in PHC in Stockholm were treated with RAAS-inhibitors and betablockers. Further analyses, e.g., dosage and persistence, are needed to assess the appropriateness.

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598. In-Hospital Cardiovascular Drugs Use in Acute Myocardial Infarction Patients and In-Hospital Mortality from 2004 to 2008 in Taiwan

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Background: Few nationwide population-based studies are available on the epidemiology of acute myocardial infarction (AMI) in Asian countries.

Objectives: The purpose of this study was to provide basic information for the establishment of policy related to AMI by examining the long-term trends in incidence, in-hospital cardiovascular drugs use, and 6-month mortality of AMI.

Methods: We used Taiwan's National Health Insurance Research Database to retrospectively identify hospitalized patients (≥18 years) who presented with AMI from 2004 to 2008 and observed them for 6 months after the discharge. We investigated the annual incidence, inhospital cardiovascular drugs use, and short-term mortality. We also analyzed the distribution of comorbid diseases among theses patients.

Results: Of 63,482 patients (mean age, 66.7 years), 71.3% were men. The incidence rates for AMI in 2008 were 62.8 per 100,000 persons and the rates was increasing for the 5 years. AMI incidence rates were higher among males than females and increased more in the older age groups. The case in-hospital fatality rate was high (12.3%) in 2004, and declined rapidly to 7.3% in 2008. Similarly, the case 6-month fatality rate decreased from 25.4% to 18.2%. Among these patients, 25,947 (40.9%) filled prescriptions for statins, 53,000 (83.5%) for clopidogrel, 37,382 (58.9%) for β-blockers, and 45,221 (71.2%) for angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers during the AMI hospitalization. The use of statins increased from 2004 to 2008 (32.1–50.1%), less so for clopidogrel (72.1–91.6%) but the prescription rates of others did not show any trend. The use of percutaneous coronary intervention steeply raised from 1999 to 2008 (40.5–58%), but not for coronary artery bypass surgery (5.0–6.2%).

Conclusions: The present study demonstrates the steady trend of an increasing incidence, but decreasing short-term mortality, for AMI in Taiwan over the past 5 years. Increasing applications of percutaneous coronary intervention, dual-antiplatelet agents and statins possibly explained improving short-term AMI prognosis.

599. Utilization of Lipid Lowering Drugs in Hungary between 2005 and 2010: Cost and Benefit

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Background: Mortality rate of cardiovascular diseases in Hungary are among the highest values in Europe. Elevated cholesterol level increases the risk of cardiovascular morbidity and mortality. The reduction of the cholesterol level with the use of lipid lowering medication can decrease cardiovascular mortality.

Objectives: The aim of the study was to analyze the changes in the utilization of lipid lowering drugs in Hungary for the period of between 2005 and 2010, access cost and analyze the trends in the changes of cardiovascular mortality rates.

Methods: Crude national drug utilization data was obtained from the administrative drug dispensing database of the Hungarian National Health Fund Administration (HNHFA) regarding the years between 2005 and 2010. Data were analyzed according to the ATC/DDD (WHO) methodology. Data were expressed as defined daily doses per 1,000 inhabitants per day (DDD/TID).

Results: During the studied 6-year period, the utilization of lipid lowering drugs (C10) more than doubled, it was 41.287 DDD/TID in 2005, and 89.091 DDD/TID in 2010. The use of fibrates varied between 6.251 and 7.990 DDD/TID, while the use of statins continuously increased from 33.142 DDD/TID in 2005 to 78.533 DDD/TID in 2010. Simvastatin was the most frequently used lipid lowering drug in 2005 with 17.300 DDD/TID, while in 2010 the most widely used lipid lowering medication was atorvastatin with 50.295 DDD/TID. In 2010 over 1 million patients (10% of the total population) received lipid lowering medication. Each year about 8% of the total reimbursement budget of the HNHFA was spent on lipid lowering medication, in 2010 it was around 100 million euros. Cardiovascular mortality rates showed a declining trend: in 2005 it was 703/100,000 inhabitants, while in 2009 it was 647/100,000 inhabitants.

Conclusions: The use of lipid lowering medications steadily increased, while at the same time the cardiovascular mortality rates decreased. This decreasing trend of cardiovascular mortality rate justifies the vast increase in the use of lipid lowering drugs.

600. Abstract withdrawn by author.

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601. Performance Measures of Diabetes Management Do Not Always Predict Better Glycemic Control: The Need for Case-Mix Adjustment

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Background: Performance measures are used for assessing quality of care. It is expected that higher performance on these measures predicts better patient outcomes but this can be influenced by patient characteristics.

Objectives: The aim of our study is to assess which performance measures for glucose management predict better glycemic outcomes and whether this is affected by case mix.

Methods: We conducted a prospective cohort study of 15,394 patients with type 2 diabetes from 2007 to 2009, using the Dutch primary care GIANTT database (Groningen Initiative to ANalyse Type 2 diabetes Treatment). We selected commonly used or proposed performance measures of glucose management which assess frequency of HbA1c-testing, glucose-regulating treatment and treatment intensification. The association between each measure and glycemic control was tested using multiple linear regression adjusting for confounders, showing estimated change in HbA1c with 95% confidence intervals (95% CI). Sensitivity to case-mix was examined by looking at interactions with patient characteristics.

Results: Better glycemic control was observed in patients with an annual HbA1c test vs. those that had no such test (HbA1c -0.30%; 95% CI -0.37 to -0.22). However, this relation was absent in those patients with lower baseline HbA1c levels, higher age and without macrovascular comorbidity. Receiving glucose-regulating treatment was only significantly associated with glycemic control in patients with a baseline HbA1c >7.3%. Treatment intensification in case of HbA1c >7% was associated with a significant improvement in HbA1c (-0.18; 95% CI -0.23 to -0.12). The improvement was larger in patients with baseline HbA1c >8.5% (-0.50; 95% CI -0.77 to -0.24).

Conclusions: Measures of treatment intensification in patients with poor glycemic control are valid instruments to assess the quality of care in the diabetes population. Measures of annual HbA1c monitoring and current treatment, however, should be conditioned or adjusted by the baseline HbA1c since they are not predictive of glycemic control in well-controlled patients.

602. Utilization of Antidiabetic Drugs among U.S: Adults, 2002–2011

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Background: During the last decade, several new antidiabetic drugs (AD) have entered the U.S. market amid increasing prevalence of diabetes mellitus. Among these were DDP-4 inhibitors (sitagliptin, approved in 2006; saxagliptin, 2009; linagliptin, 2011) and GLP-1 analogs (exenatide, 2005; liraglutide, 2010).

Objectives: To describe the U.S. market trends for prescription (Rx) AD – insulin and non-insulin ADs (NIAD) – in terms of volume, market share, and type of newly initiated drugs.

Methods: We queried the IMS Health, Vector One® National and Total Patient Tracker databases for Rx AD use for the U.S. adult population, ages 20–85 years, during 2002–2011. Data are nationally projected based on retail Rx activity. Initial therapy was defined as an AD Rx preceded by 12 months of no use of any AD. No statistical tests were performed.

Results: Between 2002 and 2011, patients prescribed ADs increased 39% (13.2 million to 18.4M adults) and Rxs increased 45% (105.6M to 152.8M). In 2002, 83.5% of AD recipients were prescribed NIADs and in 2011, 86.5%. The most commonly dispensed NIAD Rxs in 2011 were single ingredient (SI) metformin (47.6% of all NIAD Rxs), SI glipizide (11.9%), and SI glimepiride (8.7%). Among glitazone-containing products, Rxs for rosiglitazone products declined from 50.0% in 2002 to 4.9% in 2011. The class of DPP-4 inhibitors (SI or combination products) represented 9.1% of all NIAD Rxs, most of them sitagliptin (9.1M Rxs, 83.2% of all DPP-4 inhibitors Rxs). Daily injectable GLP-1 analogs represented 2.2% of NIAD Rxs, evenly divided between exenatide and liraglutide. The most common newly initiated NIAD therapy in 2011 was SI metformin (62.5% of initial NIAD Rxs) followed by SI glipizide (8.9%). About 5% of NIAD initiations were with sitagliptin-containing products. Among patients who started therapy with a glitazone in year 2011 (4.7%), 95.6% used pioglitazone-containing products.

Conclusions: From year 2002 through 2011, the AD market has increased in both numbers of patients and Rxs. Rosiglitazone experienced substantial decline in market share. The new class of DPP-4 inhibitors captured greater market share than the daily injectable GLP-1 analogs.

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603. Autonomous Region Variations in Use and Cost of Antidiabetic Drugs over Time

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Background: Over the last years, the changes in therapeutics of Diabetes Mellitus have affected the use and cost of antidiabetic drugs in a different way, and divergent trends have been observed among and inside European countries.

Objectives: To analyze variations in use and cost of Antidiabetic drugs depending on the Autonomous region within Spain.

Methods: Information from the prescriptions of A10 "Drugs used in diabetes", including A10A "Insulin and analogues" and A10B "Oral Hypoglycemic Agents" (OHAs) dispensed along 2000–2008, were obtained from the National Prescription Database of the Spanish Agency of Medicines. We followed the International Methodology of WHO to obtain comparable data, and calculated the DID (Defined Daily Dose/1,000 inhabitants/day) and CID (constant cost/1,000 inhabitants/day; year of reference 2008). The National and Autonomous Region populations -reported on January 1st for every year- were obtained from Statistics National Institute of Spain. Linear regression was considered to establish DID/CID correlation.

Results: Results: In 2000, northern and central regions presented lower values for DID and CID (28–39 DID; 13–18 CID) while southern regions showed higher values for both parameters (44–57 DID; 21–25 CID); but the use and cost were linearly correlated ($R^2 = 0.909$). At the end of the period, dispersion grew ($R^2 = 0.802$), specially in southern regions disturbing the pattern. Andalusia, Catalonia and La Rioja went down in their expected use and cost values. Murcia presented the highest values during the period for both parameters and Madrid the lowest ones. Regarding antidiabetic subgroups, Canarias showed the highest use and cost for insulin (20.2 DID and 29.2 CID in 2008), and Murcia the highest for OHAs (66.5 DID and 24.9 CID in 2008). Moderate growths can be observed in Madrid, Navarra and Baleares for OHAs use; in La Rioja and Andalusia for OHAs costs; and in Castile-Leon, Madrid and Baleares for insulin use and cost.

Conclusions: North/south differences in Antidiabetic use and cost in Spain have lost definition during the period 2000–2008. Disturbing outcomes from Canarias and Murcia made them clear candidates to interventions on management of antidiabetic drug treatment.

604. Benefit ? Risk Preferences of Patients for New Drugs To Treat Type II Diabetes Mellitus

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Background: In the Summer of 2011 use of pioglitazone was banned in some European countries. Other countries did not take such strong measures as the risk of bladder cancer – an increase from 4 to 6 cases per 10,000 patient years – was considered small and of uncertain nature. It is unknown how type II diabetes mellitus (T2DM) patients value such severe risks in the context of other harms and benefits of antihyperglycemic agents (AHA).

Objectives: Assess the perceived relevance of benefits and harms of new AHA by T2DM patients.

Methods: A stated choice survey was administered to 315 T2DM patients, aged 60–75. Patients were recruited through their community pharmacies. Eighteen choice sets (fictional drugs) were created from drug attributes with varying levels of: HbA1c control, risk of cardiovascular disease, weight, risk of gastro-intestinal symptoms, and risk of hypoglycaemic episodes. These attributes were indicated as relevant in interviews with patients and healthcare professionals and literature. In addition, all fictional drugs had either the baseline or increased level of risk of bladder cancer. Patients were presented with 6 choice sets each and asked to indicate which of the two they preferred. Analysis was done using conditional multinomial logit.

Results: Response was 226 (72%), with mean age 67 (SD: 4.5) years and 48% women. Self-reported HbA1c was 6.8% (SD: 1.1), mean duration of diabetes 9.1 years (SD: 8.1) and mean BMI 29.0 (SD: 4.4). Fifty-one (23%) patients had experienced adverse drug effects (ADEs) from their current AHA. Patients prioritised attributes in the following order. Long-term GI problems (β: -1.85, SE: 0.23) > frequent hypoglycaemia (β: -1.53, SE: 0.38) > weight increase (β: -0.90, SE: 0.20) > CV risk increase (β: -0.74, SE: 0.26) > less frequent hypoglycaemia (β: -0.66, SE: 0.29) were seen as negative attributes and CV risk reduction (β: 0.57, SE: 0.25) as positive. HbA1c and other levels of attributes were not statistically significant including the risk of bladder cancer (β: 0.024, SE: 0.4, $p = 0.95$).

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Conclusions: Patients weigh heavily ADEs that influence their daily life. Control of glucose and a small increased risk of cancer are not as important for new drugs.

605. Agreement in Balancing Benefit and Risk of New Drugs between Patients and Regulators

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Background: Regulators approve new drugs based on an assessment of their benefit risk balance at a population level as determined in clinical trials. Subsequently, these results have to be translated to individual patients, who then have to integrate these drugs into their daily life. Little information exists on (dis) agreement in perception of benefits and risks of new antihyperglycemic agents (AHA) between these stakeholders.

Objectives: Compare the perception on benefit risk balance of new AHA by regulators and type II diabetes mellitus (T2DM) patients.

Methods: A stated choice survey was administered to 88 Dutch Medicines Evaluation Board assessors and 315 T2DM patients. Eighteen choice sets were made comparing two fictional new AHA with three levels of drug characteristics: HbA1c control (main surrogate efficacy marker for AHA), effect on the risk of cardiovascular (CV) disease, weight, gastro-intestinal complaints, hypoglycemic episodes and cancer (2 levels). These characteristics were indicated as relevant in interviews with stakeholders and literature. Regulators were presented 18 choice sets, while three groups of patients answered 6 choice sets each. They were asked each time which AHA they preferred. Analysis was done with multinomial conditional logit.

Results: Two hundred and twenty-six (72%) T2DM patients and 52 (59%) regulators responded. Long-term GI problems were most influential to both groups (Regulator; β -1.409 SE 0.3; Patient; β -1.85 SE 0.23), followed by frequent hypoglycemia episodes (R; β -0.878 SE 0.4; p; β -1.53 SE 0.38) and CV risk increase (R; β -0.723 SE 0.3; p; β -0.74 SE 0.26), all negatively influencing their choice. Both valued CV risk reduction positively (R; β 0.697 SE 0.3; p; β 0.57, SE 0.25). Patients contributed negative values to weight increase (β-0.90 SE 0.20) and less frequent hypoglycemia episodes (compared to none) (β-0.66 SE 0.29). HbA1c and other drug characteristics levels did not significantly affect stakeholders drug preference.

Conclusions: Regulators and patients have generally similar preferences for new AHA. CV risk reduction, but not glucose control is considered the most beneficial characteristic by both. Patients were more sensitive to weight increase and hypoglycemia.

606. Comorbidity and Adherence to Oral Antihyperglycemic Agents in Ireland

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Background: Adherence to oral anti-hyperglycemic agents (OAH) in patients with type 2 diabetes has been shown to increase glycemic control, reduce complications and decrease mortality. However, adherence to these drugs is often inadequate. Comorbidity is highly prevalent in patients with diabetes and may adversely affect adherence.

Objectives: To examine the effect of comorbidity on adherence among new users of OAHs in Ireland.

Methods: The HSE Primary Care Reimbursement Services pharmacy claims database was used to define a cohort of new users (no use in the previous 6 months) of any OAH (ATC A10B) aged ≥25 years from June 2009 to December 2010. Persistence was examined at 6 and 12 months post-initiation. Non persistence was defined as a refill gap of >63 days. Adherence was measured by Medication Possession Ratio (MPR) at 6 and 12 months. A cut off for good adherence was defined as MPR ≥ 80%. A comorbidity score was derived from prescriptions using modified versions of the RxRisk and RxRiskV indices. Adjusted odds ratios (OR and 95% CIs) for both persistence and adherence were determined using logistic regression, adjusting for age, sex and comorbidity score.

Results: A cohort of 21,879 new users of OAH was identified. Persistence was 73.8% and 62.2% at 6 and 12 months respectively. Men were significantly more persistent with therapy than women at 6 (OR = 1.2, 95% CI = 1.1–1.3) and 12 months (OR = 1.2, 95% CI = 1.1–1.2). Patients with high comorbidity (>3 comorbid conditions) were also significantly more likely to be persistent at 6 (OR = 3.2, 95% CI = 3.0–3.5) and 12 months (OR = 2.8, 95% CI = 2.6–3.0). MPRs were 71% and 68% at 6 and 12 months respectively. Adherence was significantly higher in men than women at 6 (OR = 1.3, 95% CIs = 1.2–1.4) and 12 months (OR = 1.3, 95% CIs = 1.2–1.4). Patients with high comorbidity were also significantly more likely to remain adherent at 6 (OR = 3.3, 95% CI = 3.1–3.5) and 12 months (OR = 3.5, 95% CI = 3.3–3.8).

Conclusions: Persistence and adherence to OAHs in this study was higher in men and in those with several comorbid conditions. Results suggest that these patients may be more aware of the medical need to continue therapy.

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607. Evaluation of the Effect of the Regulatory Action Using Electronic Medical Records Data

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Background: Electronic Medical Records (EMR) data include detailed information on medical practices which can be utilized in studies on drug safety. The Ministry of Health, Labour and Welfare (MHLW) standard for EMR data specification, called "Standardized and Structured Medical record Information Exchange," has been implemented in several hospitals. They have standardized databases which include data of diagnosis, prescribed drugs, and test results in a same format, and these data can easily be combined into a single data set. PMDA has conducted several basic studies to determine characterization of these data, and in this advanced study, we evaluate the effect of the regulatory action about drug safety. This is one of the pilot studies in MIHARI Project in PMDA.

Objectives: To evaluate the effect of the regulatory action on sitagliptin, one of dipeptidyl peptidase-4 (DPP-4) inhibitors, using the standardized EMR data.

Methods: The regulatory action about update of important precautions in sitagliptin's package insert was released in April 2010. It cautioned physicians that concomitant use of sitagliptin and sulphonylurea (SU) increase a risk of a hypoglycemia and consideration of decreasing dose of SU was required to reduce the risk. To evaluate the effect of this action, the standardized EMR data from six hospitals will be collected and integrated as a single data set. The data period will be between June 1, 2009 and December 31, 2011 which covers the period of before and after the action. In analysis, (1) monthly proportion of concomitant use of SU among sitagliptin users; and (2) monthly average of the daily dose will be calculated as process measures. As outcome measure; (3) incidence proportion of a hypoglycemia will be calculated. In (2) and (3), SU users without use of any DPP-4 inhibitors will be used for comparison. (4) Segmented regression analysis will be applied if enough number of patients for analysis is available.

Results: Because this study is ongoing at the time of abstract submission, the results will be presented at the conference.

Conclusions: The conclusions will be presented at the conference.

608. Utilisation and Characteristics of New Users of Oral Antidiabetes Drugs (OAD) in the UK: 2006 2010

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Background: In the UK, medication is recommended to lower glycemia if counselling to promote weight loss has not achieved A1c values lower than 48 mmol/mol. Metformin is indicated as a first therapeutic option. In non-over weight (BMI < 25) patients or if A1C is very high a sulfonylurea is considered.

Objectives: To describe the initial use of OADs in drug naive patients relative to existing guidelines, investigate treatment patterns, and to discern characteristics that may impact effectiveness.

Methods: All patients initiating an OAD between January 2006 and February 2011 were identified from the General Practice Research Database. Data were obtained at initiation of OAD; any A1c recorded in the 6 months prior to this date was used as baseline.

Results: A total of 63,060 patients initiated at least one OAD in the study period. Per UK guidelines a majority of patients initiated with metformin (88%), followed by gliclazide (8.1%), metformin with gliclazide combination (1.5%) and glimepiride (0.7%). Combination therapy usage was infrequent (2%). Compared to metformin, gliclazide patients were older (67.1 vs. 61.0 years) and had higher median A1c (70 (IQR 60–95) vs. 64 (IQR 56–74) mmol/mol). Patients who received metformin combined with gliclazide had a median A1c of 99mmol/mol (IQR 79–113). The metformin group had higher median BMI than gliclazide (31.6 vs. 26.6 kg/m^2) and the prevalence of patients who were not overweight (BMI < 25 kg/m^2) was lower (8% vs. 36%). The proportion of patients who had very high A1c (80 mmol/mol) and who were not overweight was 1.9% in the metformin group compared to 13% in the gliclazide group.

Conclusions: This study identified patterns of prescribing (OAD) that appear to align with the UK guidelines, based on the clinical characteristics of patients. In particular, patients with higher initial levels of A1c and non overweight patients were prescribed sulfonylurea as recommended. Further research to quantify the outcomes associated with this behaviour is underway.

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609. Quantifying Usage of Exenatide BID in Patients with Renal Impairment (2008–2010)

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Background: Exenatide BID has been approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It is not recommended for use in patients with severe renal impairment and should be used with caution in patients with moderate renal impairment. A Dear Healthcare Provider (DHCP) letter was issued in October of 2009.

Objectives: To quantify exenatide BID use in patients with underlying renal impairment (chronic kidney disease [CKD] stages I-V and end-stage renal disease [ESRD]), and to assess the potential impact of the DHCP letter.

Methods: Subjects were Commercial, Medicaid and/or Medicare enrollees in a large US claims database aged ≥18 years with claims evidence for T2DM and CKD/ESRD, and a comparison cohort of patients without a diagnosis or claim for CKD/ESRD between 2008Q1 and 2010Q1. The outcomes of interest were the proportion of exenatide BID initiators in each cohort per calendar quarter (3-month), and the potential impact of the DHCP letter.

Results: From 2008-Q1 through 2010-Q1, there were 87,264 CKD and ESRD patients (males 46,120 and females 41,144). Approximately 85% of all CKD and ESRD subjects were 51 year +, and <1% of subjects were <30 year. Exenatide BID initiation rates: all CKD vs. non-CKD 2008Q1 (0.32% vs. 0.40%) 2010Q1 (0.14% vs. 0.11%); CKD stage III vs. non-CKD 2008Q1 (0.50% vs. 0.37%), 2010Q1 (0.14% vs. 0.13%). Mean exenatide BID initiation rates in the entire study period: non-CKD vs. CKD stage IV (0.17% vs. 0.12%); non-CKD vs. CKD stage V (0.20% vs. 0.08%); non-CKD vs. ESRD patients (0.26% vs. 0.04%). Exenatide BID initiation in ESRD patients was low before (0.02–0.06%) and after (0.02%) the DHCP letter.

Conclusions: The overall and stage-specific exenatide BID initiation rates in T2DM patients with CKD stages I–V and ESRD decreased steadily during the study period. Exenatide BID initiation in patients with moderate to severe CKD (III–V and ESRD) was uncommon prior to and after the DHCP letter in October 2009. The FDA has removed the REMS requirement for Exenatide BID.

610. Prevalence of Comorbid Chronic Conditions in Metabolic Syndrome Patients Using Medicine Claims Data

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Background: Comorbidity increases a patient's total burden of illness and health care costs, requires more complex clinical management, and is generally associated with poor health outcomes (Vogeli et al., 2007:393). Determining comorbidity is therefore the first step toward preventive measures and cost containment.

Objectives: To assess comorbidity [defined as the presence of any of the Chronic Disease List (CDL) conditions registered in South Africa] in metabolic syndrome patients in the South African private health care sector.

Methods: A retrospective quantitative drug utilisation review was performed using medicine claims data from the period 1 January 2008 to 31 December 2008, obtained from a South African Pharmacy Benefit Management company for 974,497 patients. Metabolic syndrome was defined according to the American Heart Association/National Heart, Lung and Blood Institute criteria, as patients (n = 17,866) who had a prescription (s) for one or more drugs, from each of the following therapeutic drug classes: antidiabetics, antihypertensives, and hipolipidaemics. Comorbidity was described as the average count of CDL conditions per patient.

Results: Of 7,050 metabolic syndrome patients (39.5%, n = 17 866) had ≥1 CDL condition, at an average chronic disease count of 1.4 ± 0.63 (median 1, maximum 5) (95% CI, 1.38–1.42) per patient. Of 71.8% (n = 7 050) of patients had one CDL condition, 23.1% that had two CDL conditions, and approximately 5% of patients had ≥3 CDL conditions. CDL conditions that co-occurred most in patients with metabolic syndrome were hypothyroidism (22.7%), coronary artery disease (13.6%), cardiac failure (10.7%), asthma (7.3%), glaucoma (4.5%), dysrhythmias (4.4%), cardiomyopathy (3.7%), epilepsy (2.2%), and a combination of hypothyroidism with cardiac failure (2.1%) and coronary artery disease (1.9%, n = 7,050).

Conclusions: The relatively high prevalence of Chronic Disease List conditions in metabolic syndrome patients in the private health care sector of South Africa emphasises the importance of disease management programmes for these patients.

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611. Discontinuation of Anticoagulant Care during Admission in a Psychiatric Hospital

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Background: Continuation of coumarin therapy is important to prevent thromboembolic events. Continuation in patients during psychiatric hospitalization may be problematic due to the patient's psychiatric status and involvement of several physicians in patient care.

Objectives: To investigate discontinuation of anticoagulant care (AC) during psychiatric hospitalization.

Methods: Retrospective follow-up study in patients treated with oral anticoagulants admitted to a psychiatric hospital between January 1, 2000, and December 31, 2006. Information on oral anticoagulant use, INR measurements and patient characteristics (age, gender, type of coumarin used prior to index date (acenocoumarol/phenprocoumon), duration of hospitalization (<8; 8–20; 21–59 and ≥ 60 days), psychiatric diagnosis and ward of admission) was collected. Discontinuation of AC was defined as no oral anticoagulant dispensed during the first seven days of hospitalization and/or no INR measurement during hospitalization. Relative risk (RR) of discontinuation of AC was estimated by using Cox regression analysis.

Results: Of 125 patients, 28.8% had discontinuation of AC. For 16.8% no oral anticoagulant was dispensed during the first week and 20.0% had no INR measurement. Patients admitted to non-psychogeriatric wards had five times higher risk of AC discontinuation than patients admitted to psychogeriatric wards (58.3% vs. 10.4%; RR = 5.2, 95% confidence interval [CI] = 2.1–12.8). Patients <60 years were three times more likely to have discontinuation of AC than patients ≥ 60 years (63.6% vs. 16.3%; RR = 3.2, 95% CI = 1.4–7.2).

Conclusions: Admission to a psychiatric hospital leads to discontinuation of AC in approximately 30% of patients, with highest risk of discontinuation in patients admitted to non-psychogeriatric wards. The highly integrated nature of psychiatric and somatic care at psychogeriatric wards seems to be beneficial in prevention of discontinuation of AC during psychiatric hospitalization.

612. Predictors of Non-Adherence to Statins: Population-Based Restrospective Cohort Study

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Background: Low levels of adherence have been documented in patients with vascular disease but studies assessing predictors of non-adherence have shown inconsistent results.

Objectives: To assess predictors of non-adherence to statins from a population perspective in a high risk cardiovascular individuals.

Methods: Design: population-based retrospective cohort using primary care data from Catalonia. Participants: all new statin users >35 years with ankle-brachial index ≤ 0.9 in 2005–2010 within the Information System for the Development of Research in Primary Care. Non-adherence was defined as proportion of days covered $\leq 50\%$. We defined short-term (6 months) and medium-term (24 months) non-adherence.Logistic regression analysis was performed to determine predictors of non-adherence to statins.

Results: Patients included: 2667. Mean age (SD): 68.9 (11.4), 62.7% were male. In the short term 35.7% of patients did not adhere to the treatment and in the medium term 62% of patients were non-adherers. Independent predictors of short-term non-adherence were: price of the statins (OR per 100€ change:1.08, CI 95% 1.02–1.14), symptomatic peripheral disease (OR: 0.69, CI 95% 0.58–0.84) and AMI (0.60, 0.46–0.79), LDL-cholesterol levels (0.996, 0.993–0.998), diabetes (0.79, 0.65–0.96), HTN (0.68, 0.56–0.82), hypercholesterolaemia (0.76, 0.64–0.90), treatment complexity (1.06, 1.01–1.11), and number of visits (0.98, 0.96–0.99). Predictors of medium-term non-adherence were: HTN (0.77, 0.63–0.93), hypercholesterolaemia (0.82, 0.69–0.97), AMI (0.62, 0.48–0.80), treatment complexity (1.10, 1.05–1.16), and number of visits (0.91, 0.90–0.93).

Conclusions: Statin adherence remains suboptimal both short and medium-term. The price of statins is an independent predictor only in short-term non-adherence. Patients with diabetes, HTN, hypercholesterolaemia, symptomatic peripheral disease, AMI and higher number of visits to their physician were less likely to be non-adherers whereas patients with more complex treatment profiles were more likely to be non-adherers. Interventions in primary care should be developed to improve medical adherence so that patients can benefit from the full protective effects of statins.

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613. The Evaluation of Appropriateness of Therapy after Percutaneous Coronary: Intervention in the Lazio Region (Italy)

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Background: Patients who undergo Percutaneous Coronary Intervention (PCI) require long term therapy with antiplatelet drugs. According to scientific guidelines, after PCI patients must be treated with clopidogrel for a minimum of 1 month and ideally up to 12 months after discharge, and with acetylsalicylic acid (ASA) indefinitely (dual antiplatelet therapy).

Objectives: To measure the prevalence of antiplatelet drug therapy among patients undergoing PCI at discharge and long term in the Lazio Region.

Methods: All patients resident in Lazio Region who underwent PCI in 2006 and 2007 in Lazio hospital performing at least 150 PCI/year were enrolled in the study. Patients died during hospitalization were excluded. The source of data were the Hospital Information System in Lazio region and Drug Claims Information System. Discharge prescriptions of a random sample of patients were extracted from hospital charts and linked to data from Health Information System. Appropriate therapy (AT) was defined as dual antiplatelet therapy (ASA and clopidogrel) with prescribed daily doses for each drug covering at least 75% of patients' individual follow-up period (6 months). Results were stratified by age groups (<65, ≥ 65 e < 75, ≥ 75) and gender.

Results: A total of 13,434 patients with PCI were included. AT was prescribed to 6013 (44.8%) PCI patients. The proportion of AT was higher in younger patients than older ones (<65 year old = 48.3%, ≥ 65 and <75 year old = 31.6%, ≥ 75 year old = 20.1%, $p < 0.01$); women were less likely to be treated with AT (38.9% vs. 46.7% for male patients, $p < 0.01$). The dual antiplatelet therapy was prescribed at discharge to 2586 (93.9%) patients on a total of 2753 examined clinical charts. The AT was changed in outpatient setting with a non appropriate therapy in 1357 (52.5%) of these patients.

Conclusions: Our results suggest that discharge prescriptions mostly provide an appropriate therapy but the proportion of PCI patients appropriately treated after discharge is suboptimal in the Lazio region, and elderly patients and women are less likely to receive appropriate therapy.

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616. The Utilisation of Ivabradine in General Practice in England; Focus on Compliance with Licence

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Background: The anti-anginal ivabradine (Procoralan™) reduces heart rate (HR) by inhibiting the sino-atrial node's funny current (I_f). It was licensed in Europe in October 2005 for chronic stable angina (CSA) with normal sinus rhythm (NSR) and a contraindication or intolerance for beta blockers (BBConI). In October 2009 a licence extension allowed concurrent beta blocker use. A Modified Prescription-Event Monitoring (M-PEM) study was conducted for post-marketing surveillance.

Objectives: To describe utilisation characteristics and to examine off label use in patients prescribed ivabradine in England under real-life primary care conditions, prior to the licence extension.

Methods: This study used an observational single exposure cohort design. Exposure data were collected from dispensed prescriptions issued by General Practitioners (GPs) from November 2005 to May 2009. Outcome data (indication, prescriber, patient demographic, clinical characteristics) were collected by sending questionnaires to GPs 6 months after each patient's first GP prescription. Summary descriptive statistics were calculated. Percentages presented exclude missing data.

Results: The evaluable final cohort consisted of 4624 patients. Median age = 68 year (IQR 60–77), 57.6% (2663/4624) male. Ivabradine initiated by hospital specialist in 82.8% (3683/4447). Starting dose 5mg bd (as per SPC) in 74.7% (3300/4418). Indication affirmed to be CSA in 80% (3204/4007). BBConI in 56.6% (2352/4159). HR measured prior to starting in 77.1% (1693/2195) of these 84.3% (1428/1693) had NSR. Other indications reported include tachycardia (4.9%,227/4624) and myocardial infarction (2.9%,136/4624). Ivabradine stopped in 33.3% (1542/4624); 1551 reasons for stopping given for 1155 patients; most common; "not effective" (9.7%,112/1155) and cardiac surgery (9.2%,106/1155).

Conclusions: Ivabradine was mostly initiated by hospital specialists for CSA at the recommended starting dose. NSR was present in the majority where HR was measured. The reported prevalence of BBConI suggests lower prescriber compliance with this requirement. High hospital initiation rates may explain frequently missing pretreatment HR data in GP records.

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617. Utilisation and Tolerability of Aliskiren; Final Results of a Prescription Event Monitoring Study

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Background: The renin inhibitor aliskiren (Rasilez®) is licensed for essential hypertension and was launched in the UK in August 2007. In clinical trials diarrhoea was a common ADR but angioedema (a known ADR with other Renin Angiotensin System drugs), occurred rarely. As aliskiren is first in its class, a Prescription Event Monitoring (PEM) study was performed.

Objectives: To describe the utilisation characteristics and tolerability of aliskiren in patients in England under real life primary care conditions.

Methods: This study used an observational single exposure cohort design. Exposure data were collected from dispensed prescriptions issued by General Practitioners (GPs) from February 2008 to November 2010. Outcome data (demographic, utilisation, and adverse events) were collected by sending questionnaires to GPs 6 months after each patient's first prescription. Summary descriptive statistics were calculated. Percentages presented exclude missing data.

Results: The evaluable final cohort consisted of 6385 patients. Median age 68 year (IQR 59–76), 44.2% (2821/6385) male. Indications: hypertension in 93.3% (5958/6385), chronic renal failure in 1.4% (90/6385) and diabetes mellitus in 1.1% (68/6385) Starting dose 150mg as per SPC in 89.7% (5389/6007), Aliskiren reported effective in 77.4% (3888/5024). There were 362 ADRs reported in 258 patients. Commonest specified ADRs: diarrhoea (7.2%, 26/362) and malaise (6.4% 23/362). Angioneurotic oedema and oedema face had 2 reports each (both 0.6%, 2/362). Aliskiren stopped in 31.0% (1858/5995). There were 2388 reasons for stopping (RFS) in 1829 patients. Commonest RFS: not effective (16.6%, 397/2388), diarrhoea (5.2%, 123/2388). Angioedema was RFS 5 times (0.2% of RFS). There were 100 deaths during the study (1.6% of cohort). Where cause of death was specified, the majority were cardiovascular in nature (44.7%, 34/76) followed by neoplasms (18.4%, 14/76).

Conclusions: Aliskiren was prescribed for hypertension in the vast majority of patients. Off label use was infrequent. Angioedema was both uncommon and uncommonly a RFS. Aliskiren was well tolerated but diarrhoea that was uncommonly a RFS in clinical trials, was a common RFS in this cohort.

618. The Prescribing of Fibrates in General Practice in the UK and the Impact of Regulatory Advice

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Background: Fibrates are used as a preventative measure against cardiovascular disease. In 2007, after review of their efficacy and safety, and in view of the role of statins, the Commission for Human Medicines concluded that fibrates should only be used first line for isolated severe hypertriglyceridaemia and only for raised cholesterol when statins can not be taken. Fibrate use alongside a stain may be of use when statins alone have not reduced triglycerides or HDL-C but the use of gemfibrozil with a statin should be avoided. This was also communicated after further review by the EMA in 2010.

Objectives: To examine the prescribing trends of fibrates in general practice in the UK in relation to regulatory advice.

Methods: Data on patients with a fibrate prescription 2000/10 were extracted from the General Practice Research Database. Patients were considered new users if they had been registered for 365+ days prior to their first prescription.

Results: Overall, fibrate use almost doubled 2000–2010, primarily due to an increase in use in patients aged 70+ years. However, no increase in the number of patients newly starting a fibrate was seen. The most commonly used fibrate was bezafibrate (˜50% of fibrate use) although there was an increase in the use of fenofibrate (13% of use 2000 to 44% 2010). In 2000, 46% of patients starting a fibrate did so as first line treatment. By end 2010, only 7% of patients starting a fibrate did so first line. Very few patients (<1% in 2010) adding a fibrate to a statin were prescribed gemfibrozil.

Conclusions: In the last decade, there has been an increase in the prevalence of fibrate use but little change in the incidence of new users. However, they have been increasingly used as second line lipid lowering therapy. It is reassuring that the use of fibrates in new patients is in line with recommendations although trends were ongoing prior to communications from regulatory authorities. This is likely in part due to the increased popularity of statins but also due to the availability of literature regarding the efficacy and safety of fibrates from other organisations. The impact of further communication at the end of 2010 remains to be investigated.

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619. Racial and Gender Disparities in Lipid-Lowering Medication Use: Results from the Multi-Ethnic Study of Atherosclerosis (MESA)

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Background: Evaluating disparities in health care is an important aspect of understanding differences in disease risk.

Objectives: To estimate race/ethnic and gender disparities in the use of lipid lowering medications (LLM) in a United States population.

Methods: MESA is a population based cohort study of 6,814 participants aged 45–84 years free of clinical cardiovascular disease. The participants self-identified as White, African-American, Hispanic, or Chinese and were recruited from 2000 to 2002. Prevalence ratio (PR) regression was used to model LLM use at baseline as a function of traditional cardiovascular risk factors, and estimated pre-treatment cholesterol. For those on LLM at baseline, pre-treatment cholesterol was estimated using a model relating pre and post treatment cholesterol observed among a subset of new medication users. This methodology is used to help control for confounding by indication.

Results: Hispanics had a significantly lower prevalence of LLM use, even at the same risk factor profile and estimated pre-treatment cholesterol (PR = 0.74 relative to whites, $p < 0.001$). This was largely explained by lack of health insurance. At the same risk factor profile, women and men did not have significantly different rates of LLM use (PR 1.13, $p = 0.11$), however there were differences in risk factor associations by gender. The prevalence of LLM use went up significantly with age in both genders, but more strongly in women (PR 1.28 per 10 years in women, 1.10 in men, $p < 0.001$ for interaction). Hypertension was also strongly associated with LLM use in both genders (PR 1.81, $p < 0.001$), but diabetes was only associated with higher LLM prevalence in women (PR 1.58 in women, 1.11 in men, $p = 0.03$ for interaction). HDL cholesterol was only associated with a lower prevalence of LLM use in women (PR 0.94 per 10 mg/dL in women, 1.00 in men, $p = 0.04$ for interaction).

Conclusions: Racial disparities exist in the treatment of cholesterol. Hispanics were significantly less likely to be on LLM at the same level of risk factors. Risk factors have differential associations with LLM use depending on gender.

620. Interrupted Time Series Analysis on the Impact of Dronedarone Authorisation on Italian and Swedish Antiarrhythmic Prescriptions

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Background: Dronedarone was recommended as a first-line agent in non-permanent atrial fibrillation by major guidelines, while Health Authorities recommended it as a second-line treatment. This discrepancy prompted us to investigate the impact of dronedarone on the prescriptions of antiarrhythmics, namely amiodarone.

Objectives: To evaluate whether dronedarone authorisation impacts on antiarrhythmic prescription in Sweden and Italy.

Methods: Prescriptions of Class I and III antiarrhythmics (ATC C01B), expressed as Daily Dose per Thousand Inhabitants per day (DDD/TID), were monthly collected from pharmacy reimbursed databases of a Northern Italian district (4.4 million inhabitants), and Sweden (9.4 million inhabitants). Sweden and Italy data were compared in terms of monthly trends of overall antiarrhythmic and amiodarone consumption. Effect of dronedarone marketing entry on antiarrhythmic prescriptions, in particular on amiodarone, was evaluated by the interrupted time series analysis. A 12-month period before and after the date of dronedarone local authorisation was selected: May 09–May 11 in Sweden, September 10–September 11 in Italy. Trend change (Tc) between the two segmented periods were estimated and was considered statistically significant when p value was <0.001.

Results: In Italy, the overall consumption of antiarrhythmics was six times as high as in Sweden (7.6 vs. 1.2 DDD/TID). In the first year on the market, dronedarone represented 1.0% in Italy and 10.7% in Sweden of the overall antiarrhythmics. In Sweden, dronedarone authorisation generated an increase in the prescription trend of antiarrhythmics ($T_c = +0.02$; $p < 0.001$) without variation in amiodarone utilisation ($T_c = 0.00$; $p < 0.001$). In Italy, dronedarone marketing had no influence on prescriptions of either antiarrhythmics as a whole ($T_c = +0.01$; $p = 0.83$) or amiodarone ($T_c = 0.00$; $p = 0.85$).

Conclusions: Although Italy and Sweden differ substantially in terms of overall antiarrhythmic use, prescription of amiodarone was not affected by the entry of dronedarone in either country. Thus, the use of these two drugs

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seems to be in line with regulatory recommendations rather than with clinical guidelines.

621. Treatment Quality Indicators Predict Improved Cardiovascular and Renal Risk Factor Control in Diabetes Patients: A Prospective Cohort Study Using the GIANTT Database

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Background: Treatment quality is measured for audit, feedback and pay-for-performance purposes. Treatment quality indicators for cardiovascular and renal risk factors in diabetes patients either measure current treatment or treatment intensification. The extent to which both types of quality indicators are associated with better patient outcomes is unclear.

Objectives: To assess whether currently used and proposed quality indicators for treatment of cardiovascular and renal risk factors predict better short-term patient outcomes.

Methods: We conducted a prospective cohort study of 15,394 patients with type 2 diabetes from 2007 to 2009, using the Dutch primary care GIANTT database (Groningen Initiative to ANalyse Type 2 diabetes Treatment). We included quality indicators of "current treatment" and "treatment intensification". The association between each indicator and the risk factor outcome was tested with multiple linear regression adjusting for confounders, showing estimated changes in systolic blood pressure (SBP), LDL-cholesterol (LDL-C), or albumin/creatinine ratio (ACR) with 95% confidence intervals (95% CI).

Results: Current treatment with antihypertensives in patients with high SBP or with Renin-angiotensin-aldosterone-system inhibitors in patients with high ACR levels did not predict better outcomes. Current lipid-lowering treatment did predict better LDL-C levels (-0.37 mmol/L; 95% CI -0.44, -0.29). Treatment intensification in uncontrolled patients was significantly associated with improvements in LDL-C (-0.84 mmol/L; 95% CI -0.95, -0.72) and ACR (-3.1 mg/mmol; 95% CI -6.16, -0.03). For SBP, only treatment intensification after 2 clearly elevated levels (> 160 mmHg) was associated with improvements in SBP (-2 mmHg; 95% CI -3.99, -0.01).

Conclusions: Indicators of "treatment intensification" are better instruments to assess quality of risk factor treatment than indicators of "current treatment", since the latter do not predict much improvement on short-term patient outcomes. For high blood pressure, one should best focus on measuring treatment intensification in patients with repeated elevated SBP levels.

622. Trends in the Consumption of Antihypertensive Therapy in Portugal, 2004–2011

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Background: In Portugal, the diagnosis and control of hypertension (HT) is of particular importance, given that cerebrovascular disease is the first cause of disability and death. In Portugal, the ESH/ESC Guidelines have been considered a reference for the treatment of HT. However, deviation from guidelines contributes to the high cost of medications and may generate difficulties in providing affordable drugs, thus it is essential to know the pattern of antihypertensive (AHT) drugs used.

Objectives: To determine the trends in the consumption of AHT over the 8 years period (2004–2011).

Methods: Drug consumption data (therapeutic subgroups selected CO2, CO3, CO7, CO8 and CO9) was estimated for the study period through the 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 1,000 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 AHT. A GLM model was adjusted to explore regional asymmetries in drug consumption.

Results: The total DHD increased linearly (beta = 13.1; R^2 = 0.86;p = 0.001) from 248.4 in 2004 to 344.8 in 2011 (total growth of 38.8%), mainly due to agents acting on the renin-angiotensin system use. Over the period, angiotensin II antagonists (ARB) increased significantly and the ratio ARB/(ACE inhibitors + ARB) in DDD rose from 33.8% to 51.9%. Cost analysis showed that since 2004 the total expenditure rose from 457M to 483M. The cost/DDD decreased from 0.48 to 0.36€, due to the growth of the market share of generics and gov. decisions to reduce the price of both generics and branded products.

Conclusions: Consistent with the reported increase in the prevalence and awareness of HT, the consumption of AHT rose between 2004 and 2011. The higher utilization rates of ARB showed the diminutive impact of guidelines in Portugal so far. The recent Memorandum of Understanding signed between the Portuguese Gov. and Troika (IMF,EC,ECB) imposed several prescribing guidelines to achieve rational prescribing and expenditure control, which include HT guideline (December 11).

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623. Treatment Duration of Dual Antiplatelet Therapy and Re-Hospitalization for Acute Coronary Syndrome after Percutaneous Coronary Intervention

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Background: Optimal treatment duration of dual antiplatelet therapy after percutaneous coronary intervention (PCI) remains uncertain.

Objectives: The objective of this study was to determine the association between duration of dual antiplatelet use and the risk of acute coronary syndrome (ACS) re-hospitalization in a cohort of ACS patients undergone PCI.

Methods: We identified 975 patients newly diagnosed of ACS and underwent PCI between July 2007 and June 2009 at a medical center in Taiwan. Cox proportional hazard models were used to examine the association between treatment duration of dual antiplatelet therapy and hazards of ACS re-hospitalization.

Results: At a mean follow-up of 2.3 years, the use of clopidogrel for ≥9 months provided non-statistically significant benefit in reducing hazards of ACS re-hospitalization (adjusted HR 0.69, 95% CI 0.48–1.00; p = 0.05), while those with ≥12 months treatment experienced statistically significant clinical benefit (adjusted HR 0.59, 95% CI 0.36–0.95; p = 0.03). However, clopidogrel therapy ≥15 months was not associated with a decreased hazard of ACS re-hospitalization (adjusted HR 0.57, 95% CI 0.29–1.13; p = 0.11). Similar results were found in the DES population, but to whom the 12 months of clopidogrel therapy is especially critical.

Conclusions: The benefit of use of clopidogrel for ≥12 months in reducing the risk of ACS re-hospitalization was significant among ACS patients underwent a PCI, and was especially critical to those underwent DES. These findings also support the latest clinical guideline recommended by American College of Cardiology/American Heart Association.

624. Dronedarone Associated Pulmonary Toxicity and Prior Amiodarone Exposure: A Pharmacovigilance Analysis

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Background: Dronedarone is a benzofuran derivative of amiodarone. Pulmonary toxicity is a well-recognized adverse effect of amiodarone. FDA received reports of pulmonary toxicity in patients on dronedarone with prior amiodarone exposure.

Objectives: To assess a safety signal of pulmonary toxicity with dronedarone and if prior amiodarone exposure is a risk factor.

Methods: We evaluated the FDA's Adverse Event Reporting System (AERS) database to identify case reports of pulmonary toxicity with dronedarone from 1 July 2009 to 22 December 2010. Cases were adjudicated based on a case definition and assessed for clinical characteristics. IMS Health, Vector One®: Concurrency (VOCON) was used to assess the frequency of prior amiodarone use in dronedarone-treated patients. We obtained non-national estimates (sample) of patients with prescription claims for amiodarone and dronedarone within 60 days of each other during the cumulative time period from July 2009 through January 2011. The fill sequence between dronedarone and amiodarone prescription claims was also determined.

Results: AERS received 1,365 adverse event reports with dronedarone within 18 months of approval. We identified 23 cases of pulmonary toxicity, reported primarily as interstitial lung disease. Fourteen of 23 cases (61%) reported prior amiodarone exposure. In the sample of patients used to assess concurrency, around 73,500 patients had a dronedarone prescription claim. Only 9% of patients had an amiodarone prescription claim within 60 days prior to the dronedarone prescription claim.

Conclusions: The assessment of postmarketing data identified a safety signal for pulmonary toxicity with dronedarone with some cases indicating prior use of amiodarone. Limitations of AERS data include under-reporting and reporting bias. Drug utilization patterns also showed prior exposure of amiodarone in a sample of dronedarone users. Variation in time intervals used for prior exposure may produce different results. Further studies are needed to assess if prior amiodarone exposure is a risk factor for dronedarone associated pulmonary toxicity.

625. Prescription Pattern Monitoring in South Korea during 2009–2010 Using WHO-ATC/DDD Tool

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Background: Reasonable safety measures for marketed drugs requires the understanding of current state of national drug utilization and prescription pattern.

Objectives: To grasp the overall pattern of prescription of drugs in South Korea, especially using WHO-ATC/DDD tool.

Methods: *Design*: drug utilization research, descriptive statistics (prescription event monitoring). *Setting* : prescriptions issued and claimed during 2009.01.01. ~2010.12.31. from HIRA administrative database (phar-

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macy benefit claim data). *Exposure or intervention*: prescribed drugs by patient's age group or sex. *Main outcome measures*: prescription frequencies/proportions (%) and DDDs/1,000 inhabitants/day by WHO-ATC classification codes, *Statistical analysis*: chi-square test.

Results: We analyzed the prescription patterns, applying to WHO-ATC classification and DDD index system using pharmacy benefit claim data from HIRA (Health Insurance Review Agency). Of 1,348 and 1,336 drugs at WHO-ATC 5th level were consumed each by year. The amount used can be analyzed upon the DDD index matched 803 and 801 drugs. Patients from 40 to 80 years old comprised a large proportion of overall drug consumption. As a result of an in-depth analysis of antihypertensive drugs, 93 depressants were prescribed in 2010 and the quantity consumed was 128 DDD/1,000 inhabitants/day.

Conclusions: In South Korea, various products were administered due to the diverse spectrum of marketed drugs. And the majority of marketed drugs were coded with WHO-ATC classification code and DDD index at the product level. So drug utilization monitoring by WHO-ATC/DDD system was easier than our expectations.

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628. Profile and Costs of Dyslipidemic Patients Served by the Unified Health System, Brazil

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Background: Lipid disorders can be considered a public health problem of great importance and drug therapies for its control are continuous use and expensive.

Objectives: Describe the costs and the demographic and epidemiological profile of patients with dyslipidemia treated by the Unified Health System (SUS), in the period 2003–2006.

Methods: Historical cohort of dyslipidemic patients who started treatment in SUS, from January 2003 to December 2006, and had at least three records of expenditures in the first half of follow-up, being the first record relating to a hypolipidemic. The selected explanatory variables were: sex, age, region of residence, diagnosis and drug used. The average monthly expenses individual (dependent variable) was obtained by sum of the individual costs drugs in the first year of treatment divided by the number of months in wich the patient remained in treatment. We performed a descriptive analysis and a multivariate analysis in order to assess the association between the average monthly individual and other variables. A linear regression model was constructed including all variables and by taking sequential deletion in accordance with the statistical significance.

Results: Pure hypercholesterolemia was the main diagnosis registered. Higher frequency was observed in women adult, elderly and residents in Southeast Brazil. The drugs most used were simvastatin and atorvastatin, with individual monthly average expenditure of approximately R$6,800. It was observed that increasing age led to lower spending, that males patients tended to spend more and that atorvastatin is the drug that most promoted impacted in the monthly expenses.

Conclusions: The epidemiological profile observed was consistent with the literature. The average individual spending was high (about 12% of the minimum wage), considering the average family income in Brazil. Changes in lifestyle, access to drugs more effective and appropriate guidelines on use of drugs should be emphasized to the risk group identified in this study, in order to change this scenario, preventing the occurrence of cardiovascular diseases, and the rationalization and optimization of scarce public resources available.

629. Pro-Arrhythmic Risk of Oral Antihistamines (H1): Combining Adverse Event Reporting Data with Drug Utilization Data across Europe

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Background: Pilot study, carried out as part of ARITMO project, evaluating the pro-arrhythmic risk of antihistamines (Ahs – R06AA, AB, AC, AD, AE, AX).

Objectives: Analyze FDA Adverse Even Reporting System (FDA_AERS) alongside drug utilization from across Europe (15 countries).

Methods: Spontaneous reports of QT prolongation and Torsades de Pointes (TdP) associated with AHs were retrieved in the FDA_AERS (2004–2010 period). A disproportionality signal was defined by a Reporting Odds Ratio (ROR) significantly >1 and cases ≥ 3. The Ari-

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zona_CERT website was used to identify unexpected signals (www.azcert.org). Consumption data provided from administrative databases – mainly reimbursed.

Results: AHs reported in 109 cases of TdP/QT prolongation and six drugs resulted in a disproportionality signal: alimemazine (cases = 3; ROR = 6.4; CI95 = 2.0–20.2), cetirizine (20; 2.9; 1.9–4.6), dexchlorpheniramine (7; 4.5; 2.1–9.5), diphenhydramine (24; 2.1; 1.4–3.2), fexofenadine (11; 4.7; 2.6–8.6) and loratadine (19; 3.9; 2.5–6.1). Only diphenhydramine is included in AZCERT lists (list III) and therefore five signals can be considered unexpected. Very variable AH utilization, e.g., in 2009: 0.92 Lithuania, 8.65 Estonia, 18.79 Slovenia, 22.64 Scotland, 37.43 France and 59.86 Norway. Total utilization higher in Serbia than reimbursed – 8.81 to 12.31 total vs. 2.00 to 3.18 reimbursed. In Sweden, lower OTC than reimbursed (10.07–11.63 OTC and 23.29–24.59 reimbursed). AHs with unexpected signals represented a very different fraction of the total AH utilization: from 29% in France to 85% in Lithuania.

Conclusions: Differences in utilisation, which may be due to differences in co-payments and prescribing restrictions, imply different levels of risk. Drugs with considerable potential for OTC require more intensive surveillance due to the lack of strict monitoring by physicians. Some drugs largely used only in a few countries also need further investigation on their proarrhythmic risk. In particular, the very high use of desloratadine and levocetirizine in France (53% of the total AH DDDs) suggests the need of specific analyses of the French spontaneous report database.

630. Attitude of Prescribing Proton Pump Inhibitors in Patients Using Clopidogrel for Secondary Prevention of Cardiovascular Events Utilizing Survey Study

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Background: Antisecretory drugs such as histamine-2 receptor antagonist (H2RA) and proton pump inhibitors (PPIs) are coprescribed with clopidogrel to reduce the risk of gastrointestinal bleeding. Although several studies have suggested that PPIs reduced the efficacy of clopidogrel in platelet aggregation assay and clinical outcomes, these effects are controversial.

Objectives: To ascertain the attitude of physicians in coprescribing clopidogrel and proton pump inhibitors.

Methods: Online surveys were sent via email to (1) primary care physicians; (2) cardiologists; and (3) gastroenterologists in nine practices of University of Pennsylvania Health System. The survey questions contained information on physician demographics, physician preferences, and confidence in coprescription of clopidogrel, H2RA and each class of proton pump inhibitors. Confidences and changes in prescribing were assessed and compared across each specialty using chi-squared (χ^2) analysis with level of significance at $p < 0.05$.

Results: Forty-seven physicians (22.8%) responded and 67% had changed the way they prescribed antisecretory drugs for patients who were taking clopidogrel. Of 61.5% of primary care physicians had low confidence in using PPIs for prevention of gastrointestinal bleeding in patients on clopidogrel, while 66.7% of gastroenterologists were usually confident in using PPIs in patients using clopidogrel. Although 60% of cardiologists and primary care physicians would switch from PPIs to H2RA if their patients needed clopidogrel, 90% of gastroenterologists would continue using PPIs in clopidogrel users. However, we could not generate a statistically significant difference among specialties due to a small sample size.

Conclusions: There are differences in the interpretation of existing data on PPIs and clopidogrel by medical specialty: primary care physicians have the most concern about coprescribing and, along with cardiologists, were more likely than not to switch from PPIs to H2RAs in patients requiring clopidogrel. In contrast, gastroenterologists were confident in using PPIs with clopidogrel and would rarely switch.

631. Have Increases in Co-Payments for Medicines Further Burdened Australians in Remote and Disadvantaged Areas?

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Background: To determine whether the national declines in prescription medicine use occurring after the Co-payments for publically-subsidised medicines in Australia were increased by 21% in 2005. Use of many medicines fell at the national-level after this rise in co-payments.

Objectives: To determine whether the 21% increase co-payments impacted on all areas of Australia or was specific to remote and disadvantaged areas.

Methods: Observed dispensing of proton pump inhibitors (PPIs) and statins were obtained for 1392 statistical local

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areas (SLA) of Australia in 2004 and 2006. Ratios of observed/expected dispensing (dispensing ratios) for each SLA were calculated. Expected dispensing was based on national dispensing rates and age-standardised to each SLA. Expected dispensing for 2006 was based on pre-2005 prescription trends. Mean dispensing ratios for each medicine and year were calculated for all remoteness and disadvantage groups. Generalised regression models compared the percentage change in dispensing ratios from 2004 to 2006.

Results: Between 2004 and 2006 PPIs dispensing fell significantly in major cities (-13.7%, 95% CI = -17.3 to -9.8), inner regional (-14.0, 95% CI = -19.5 to -8.2), outer regional (-14.6%, 95% CI = -19.9 to -9.0) and remote areas (-9.4%, 95% CI = -16.4 to -1.8). Statins dispensing fell in all groups but the most remote (range 6–7%). When focussing on disadvantage, PPI dispensing fell significantly in all groups (range 12–15%). Statins dispensing did not fall significantly in the most disadvantaged areas (-2.9%, 95% CI = -8.6–3.2) but did in the least and second-least disadvantaged areas (-6.5%, 95% CI = -11.3 to -1.5, and -5.8, 95% CI = -10.5 to -0.9, respectively). Dispensing of PPIs and statins in the most remote and disadvantaged areas remained substantially below levels expected for Australia after the 21% co-payments increase.

Conclusions: The findings suggest that the 2005 21% in patient co-payments adversely impacted on prescription medicine use in all areas of Australia and was not specific to remote or disadvantaged areas. Indeed, dispensing of statins fell significantly in all areas but the most remote and disadvantaged, and the existing gap in dispensing of PPIs and statins was not widened by the co-payments increase. PPIs, which are used at above-prevalence rates in Australia and have cheaper over-the-counter substitutes available, were more sensitive to co-payment increases than statins.

632. Variable Approaches to Enhancing the Prescribing of Losartan Once Generics Available; Influence and Future Direction

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Background: Multiple demand side initiatives across Europe have enhanced prescribing of generics in a class/related classes with varying degrees of success depending on nature and intensity of reforms. These include initiatives to enhance prescribing of ACEIs (typically low cost generics) vs. patented ARBs. Recently, generic losartan reimbursed offering savings if losartan replaces other ARBs. Patient care should not be compromised with successful switching between ARBs, and all ARBs seen as essentially similar.

Objectives: Analyse the influence of different demand side measures to enhance utilisation of losartan vs. patented ARBs alone or in combination to guide future health authority/health insurance activities.

Methods: (1) Time series analyses of monthly reimbursed ARB utilisation and expenditure in DDDs (2011) – C09CA01-09; C09DA01-04,06-08; C09DB01,02,04,05; C09DX01-03 – in Austria, Belgium, NHS Bury (England), Denmark, France, Ireland (GMS population), Scotland, Spain (Catalonia), and Sweden (administrative databases only) up to 3 years before generic losartan reimbursed to up 5 years after; and (2) Pertinent demand side measures recorded.

Results: Preliminary analyses show (1) losartan compromising 93% of total single ARB utilisation 18 months after delisting of other ARBs in Denmark; similarly for losartan combinations; (2) Easing of prescribing restrictions for losartan in Austria and Belgium enhanced its utilisation as first line ARB; limited switching between ARBs; (3) appreciable increase in losartan utilisation in NHS Bury (UK) and Sweden following targeted activities including switching; and (4) generally limited change in utilisation of losartan in other European countries with no specific activities.

Conclusions: Full analyses currently being conducted. Preliminary analyses suggest no or limited cross transfer of initiatives to enhance prescribing of generics first line in a class/related class, in this case generic losartan, unless specific activities undertaken. Specific measures needed including switching, prescribing targets, and easing prescribing restrictions.

633. Influence of Lifting Prescribing Restrictions for Losartan in Austria; Implications for Other Classes

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Background: Prescribing restrictions have reduced utilisation of atorvastatin and limited prescribing of ARBs in Austria. Generic losaratan recently reimbursed (October 2008) with prescribing restrictions removed for losartan but not patented ARBs. Generic oral risperidone since 2004 and generic MR venlafaxine since May 2009. How-

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ever, no specific measures encouraging oral risperidone vs. patented atypical antipsychotics (prescribing restrictions for injectable risperidone and olanzapine) – AAPs – or generic MR venlafaxine vs. patented anti-depressants (ADs). General measures to encourage generics include education and financial incentives.

Objectives: Analyse whether (1) easing of prescribing restrictions enhanced losartan utilisation vs. patented ARBs; and (2) Demand side measures increased utilisation of risperidone and venlafaxine following generics.

Methods: (1) Quasi-experimental study using a segmented time series design of monthly ARB utilisation and expenditure (Data warehouse BIG, Cube HMSTAT based on "maschinelle Heilmittelabrechnung") in DDDs (C09CA01-09; C09DA01-04,06-08; C09DB01,02,04,05; C09DX01-03) 2 years before generic losartan to 34 months after; (2) observational study AAP utilisation (DDDs) and expenditure (N05AH03-06, N05AL05, N05AX08,11-13) 2003 to 2010; (3) time series analysis of utilisation (DDDs) and expenditure of newer Ads (N06AX11,16,18,21,22) 2 years before generic venlafaxine MR to 27 months after; and (4) Demand side measures recorded.

Results: Preliminary analysis shows (1) Lifting of the prescribing restrictions for losartan enhanced its utilisation ($p > 0.001$) alongside a corresponding slowing in rate of growth in utilisation of other sartans ($p > 0.01$); (2) risperidone utilisation increased but% total utilisation AAPs decreased – 32% in 2005 to 24% in 2010; and (3) Venlafaxine utilisation increased 32% 24 months after generic MR (MAT); however % of overall Ads steady with increasing utilisation of duloxetine (128% MAT after 24 months) and agomelatine.

Conclusions: Results demonstrate lifting of prescribing restrictions increased losartan utilisation vs. other ARBs. However, variable influence of demand side measures on AAPs and ADs. Consequently more specific measures may be needed.

634. Chronic Heart Failure in the Elderly: Clinical Characteristics and Resource Utilization Following Initial Hospitalizaton

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Background: Despite advances in its management, treatment, and the identification of preventable risk factors, heart failure (HF) remains a major health problem in the US.

Objectives: To determine characteristics of and medical resource utilization following hospitalization among elderly patients with chronic HF.

Methods: Patients 65 years and older, with ≥1 hospitalization with a chronic HF diagnosis (ICD-9 428.22, 428.32 or 428.42) were identified in the MarketScan® database between 2004 and 2008. Patients were observed starting 6 months prior to index chronic HF hospitalization (IH) until disenrollment or end of data availability. Resource use during IH and subsequent 4 HF re-hospitalizations were calculated. Per patient per month (PPPM) utilization rates were calculated based on inpatient, outpatient and prescription data.

Results: A total of 5,741 patients met the inclusion criteria. At least one HF re-hospitalization was observed in 25% of patients, representing ≥85% of all-cause hospitalizations in these patients. Mean HF hospital length of stay was 6.7 days at IH and 7.2 days at fourth HF re-hospitalization. All-cause hospitalization rate was 0.03 visits PPPM during baseline and increased and remained elevated relative to baseline throughout follow-up. HF re-hospitalization rates peaked at 0.062 PPPM 3-6 months post IH. All-cause and HF-related outpatient visit rates peaked at 4.1 and 0.65 visits PPPM, respectively, within three months after IH. The proportion of patients receiving cardiovascular drugs (beta blockers, diuretics, statins) changed little during the 24 months of follow-up after IH discharge.

Conclusions: Treating elderly chronic HF patients is resource intensive. Utilization peaks in the first three months post IH. New interventions to improve health outcomes in the elderly HF population hold the potential to decrease post IH resource utilization.

635. Are Patients with Central and Branch Retinal Vein Occlusion at Increased Risk of Cardiovascular Disease?

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Background: Little research has been done on retinal vein occlusion and the risk of cardiovascular disease. We therefore wanted to study this specific research question using patient level data in a real life setting.

Objectives: To determine if there is an increase in cardiovascular comorbidities in patients diagnosed with central and branch retinal vein occlusion (CRVO, BRVO, ICD-10 codes: H348A and H348B) compared to the age and gender matched controls. This was studied through proxies, where the proportion of patients utilizing blood pressure lowering drugs, lipid lowering drugs, anticoagulantia, and antidiabetic drugs was determined.

Methods: This is a retrospective cohort study. We used the CEBRxA database, which combines data from the national Swedish drug registry, with a public claims database for the South-West region of Sweden, comprising around 1.5 million individuals. All patients with CRVO or BRVO diagnosed between 1st of July 2005 to 30th of

June 2009 were identified. We further applied a washout and excluded all patients with a history of CRVO or BRVO from 2000 to 30th of June 2005. The exposed population of CRVO and BRVO was compared to a randomly selected control group of five controls per case, matched for age and gender. The primary outcome was the utilization of blood pressure lowering drugs, lipid lowering drugs, anticoagulantia, and antidiabetic drugs. We used Fisher exact test to test the null hypothesis of no difference in drug utilization. Drug utilization was measured during the 12 months prior to the date of first CRVO/BRVO diagnosis.

Results: We identified 571 CRVO and 809 BRVO patients and found an increased utilization of blood pressure lowering drugs (OR: 1.41 for CRVO and 1.59 for BRVO, both $p < 0.01$), lipid lowering (OR: 1.25 for CRVO, $p < 0.05$ and 1.36 for BRVO, $p < 0.01$), anticoagulantia (OR: 1.85 for CRVO and 1.61 for BRVO, both $p < 0.01$), and antidiabetic drugs (OR: 1.41 for CRVO, $p < 0.05$ and 1.87 for BRVO, $p < 0.01$).

Conclusions: The CRVO and BRVO populations are at time of diagnosis a population with a higher utilization of cardiovascular drugs. This should be taken into consideration when new treatments are initiated.

636. Is There Any Difference in the Experience and Beliefs of Current and Former Statin Users?

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Background: Patients' reasons for continuing and adhering to different medicines has been widely researched, but they can vary according to medicines. Statins are used by millions worldwide to treat high cholesterol. This study was carried out on patients taking statins, a symptomless disease, using in-depth interviews to determine what makes statin users continue the treatment or not.

Objectives: To examine the experiences and beliefs of both former and current statin users about initiating and either continuing or discontinuing the treatment.

Methods: Qualitative in-depth interviews were conducted with 10 individuals who have continued statin treatment for at least 1 year and 10 individuals who discontinued statin treatment at least 9 months prior to the interview. Participants were recruited through a community pharmacy in Iceland. The interviews were transcribed verbatim and coded for emerging themes. The analysis was based on concepts from risk theory.

Results: There did not seem to be much difference between the experiences and beliefs of continuers and discontinuers. Both groups found it important to like and be able to trust their physicians, but felt the physicians did not have enough time to talk to them. Both groups felt they had not received much information about the treatment, apart from it being intended to lower their cholesterol. They would have liked the physician to explain better to them why they needed the treatment and what might happen. The continuers were more focused on receiving information on possible side-effects than the discontinuers, but both groups mentioned that knowledge of possible side-effects might prevent them from taking the medicine. The continuers claimed to take the statin because "they were told to" and the discontinuers said they would start treatment again if they were told to do so.

Conclusions: There does not seem to be much difference in the experience and beliefs of current and former statin users. The results suggest that having more time with the physician and receiving more information about the treatment might increase patients' likelihood of continuing treatment.

637. Service Provider Utilization Patterns in Patients with Type 2 Diabetes with Medicaid or Employer-Based Health Insurance Coverage

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Background: Socioeconomic status (SES) impacts many aspects of diabetes management. Many studies, especially those utilizing large automated insurance databases, do not include patient-level SES information; however, insurance type is usually available.

Objectives: To examine service provider utilization patterns of patients with type 2 diabetes mellitus (T2DM) with Medicaid (MCD) or employer-based commercial insurance (COM).

Methods: Patients aged 25–64 with a T2DM diagnosis or an oral hyperglycemic agent prescription between 2003 and 2010 were identified in a large US insurance claims database. Patients with ≥12 months of history in the database and no T2DM claims before the index T2DM diagnosis were considered newly diagnosed patients. The pattern and service provider type from claims records with T2DM diagnosis as the primary diagnosis was compared between the two insurance types.

Results: A total of 47,048 T2DM patients with relevant T2DM claims were identified; 976 patients (2.1%) had MCD and 7,299 (15.5%) were newly diagnosed. On average, T2DM patients with COM had 14.9 and MCD had 27.1 claims during the study period ($p < 0.0001$). The top five provider facilities or categories at the claims

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records level: outpatient facility (31.4%), primary care (31.2%), specialist (16.2%), home care provider (5.4%), and acute-care hospitals (2.8%). Utilization patterns were similar for newly diagnosed and prevalent T2DM patients with COM. Primary care/outpatient facility claims were most frequent in COM patients (32–36%, respectively). In MCD patients, the most frequent claims were for home care providers (34%) in prevalent T2DM patients and outpatients facilities (60%) for new T2DM patients.

Conclusions: Service provider utilization pattern and frequency differed significantly between T2DM patients with COM and MCD and by newly diagnosed or prevalent T2DM status. This differential pattern could introduce potential channeling bias in pharmacoepidemiology studies. This study suggests a need to consider using insurance type as a surrogate for SES; it may be a potential confounder in comparative studies.

638. Evaluation of a Computerised Decision Support System for Use by Non Medical Prescribers in Type 11 Diabetes

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Background: Previous studies have shown that a computerised decision support system (CDSS) can improve confidence and certainty in clinical decision making; in addition they can increase adherence to evidence based guidelines. Non medical prescribers (pharmacists and nurses) who have undertaken accredited coursesin the have the same prescribing rights as GPs. Positive results were obtained from a previous study of UK general practitioners but to date the use of a CDSS has not been evaluated with non medical prescribers.

Objectives: To evaluate the effectiveness of a computerised decision support system for prescribing for Type 11 diabetes by non medical prescribers

Methods: Purposive sampling was used to obtain a sample of 10 non medical prescribers. They were presented with a clinical vignette without and then with a CDSS. Standardised semi structured interviews were used to determine ease of decison making, confidence in decison making and confidence in the evidence behind the decision making. Results were expanded by asking the perceived advantages,disadvantages and barriers to use of the system in practice.

Results: 70% of non medical prescribers felt that the CDSS improved their decision making process.Ease of decison making improved as did confidence that the decison would result in the best output for the patient. Cofidence in the evidence behind the decision improved. The results were similar for both pharmacist and nurse non medical prescribers.

Conclusions: A CDSS has potential to improve confidence in,and outcomes from prescribing by non medical prescribers for chronic conditions.

639. Patient Characteristics at Type 2 Diabetes Diagnosis for Patients with Medicaid and Those with Employer Based Health Insurance

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Background: Socioeconomic status (SES) has been shown to impact multiple factors in diabetes management. Large automated insurance claims databases often lack patient-level SES measures, but insurance type is often available.

Objectives: This study describes the characteristics of patients with type 2 diabetes mellitus (T2DM) in a large US insurance claims database who had either Medicaid (MCD) or employer-based commercial insurance (COM).

Methods: 1,208,471 patients with T2DM diagnosis or oral hyperglycemic agent (OHA) prescription between 2003 and 2010, aged 25–64, were identified, of whom 22,380 (1.85%) had MCD. Patients with ≥12 months of history in the database with no T2DM claims before the index T2DM diagnosis were considered newly diagnosed patients. Patient characteristics and comorbidities were compared by insurance type.

Results: Compared to COM, MCD patients with prevalent T2DM were slightly younger (<40 year 23.9% vs. 14.2%, 40–49 year 29.3% vs. 26.3%, 50–59 year 32.2% vs. 41.2%, 60–64 year 14.7% vs. 18.3%, $p < 0.0001$), more likely to be female (65.3% vs. 46.7%, $p < 0.0001$), and used more triple therapy or insulin (triple therapy 15.3% vs. 14.5%, any insulin/GLP + OHA 7.4% vs. 4.2%, any insulin/GLP only 6.8% vs. 4.8%, $p < 0.0001$). In newly diagnosed T2DM patients, these trends were consistent. In prevalent T2DM patients, all complications were greater for MCD than COM patients (eg neuropathies 14.1% vs. 8.4%, renal failure 11.4% vs. 6.5%, myocardial infarction 17.6% vs. 13.5%, all $p < 0.0001$). In newly diagnosed T2DM patients, this trend was attenuated.

Conclusions: In summary, T2DM patients with MCD had important differences in characteristics and treatment patterns compared to those with COM. Insurance type is associated with multiple factors including socioeconomic status which have been shown to be associated with differences in outcomes across chronic diseases. This study demonstrates the need to understand and try to adjust for differences in patient characteristics such as socioeconomic status.

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640s Necessary Metrics for Evaluation of Coordination of Care of Individuals with Diabetes Mellitus

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Background: Periodic reporting of health statistics is a fundamental tool of public health and health care planning. We propose that an aspect of care requiring further description is the coordination of patients' care among clinicians. One patient population that is expected to benefit from care coordination is the population of adults with diabetes mellitus who have complicated medication regimens and multiple comorbid illnesses.

Objectives: We aimed to conceptualize the necessary building blocks for research about care coordination and propose how these may be measured with claims data.

Methods: We assembled a team of experts in health services research and diabetes care and cataloged the key concepts needed to describe the care coordination of individuals with diabetes. We created a compendium of measures used in the literature for each building block.

Results: We favor the definition of care coordination used by the Agency for Healthcare Research and Quality: care coordination involves numerous participants dependent upon each other to carry out disparate activities, who need knowledge about their own and others' roles and resources, and who rely on exchange of information. We identified 4 key concepts (building blocks) that must be operationalized to describe care coordination. These are (1) the identification of a patient's medical home and medical neighborhood; (2) the correct attribution of an episode of care to a unique provider; (3) the correct identification of the primary care provider; and (4) identification of care delivered within a network of providers. We note that claims data are inadequate to measure the quality or quantity of information exchanged. We discuss the strengths and limitations of the measurement approaches described for each building block.

Conclusions: These building blocks, generated with claims data, will have broad application. They might be used to generate statistical briefs describing the care coordination of individuals with diabetes, such as for comparisons across plans. These measures might be used to test hypotheses about the impact of care coordination on medication utilization, on adherence to medications, and on clinical outcomes.

641. High-Risk Prescribing of Aliskiren in Practice: Findings from the GIANTT Diabetes Cohort

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Background: Monitoring the use of new drugs in practice is important, especially when there are safety concerns. The novel direct renin-inhibitor aliskiren was registered in Europe in August 2007 as an antihypertensive. Whether combined use with other blockers of the renin-angiotensin-system (ACEi or ARB) would offer further benefit in high-risk patients was tested in the ALTITUDE trial starting October 2007. In December 2011, interim data from this trial suggested increased risks of complications in type 2 diabetics who received this drug in addition to an ACEi/ARB.

Objectives: To determine patterns of aliskiren prescribing, safety monitoring, and characteristics of diabetics who received aliskiren in clinical practice.

Methods: Observational study of 33,699 patients with type 2 diabetes from the Dutch GIANTT cohort. Data on comorbidity, risk factor levels (blood pressure, serum potassium, albuminuria, kidney function), and prescribing were collected from electronic medical records. Starting aliskiren was defined as a first prescription in the period 2008–2011. Logistic regression analysis was conducted to test for associations between patient level factors and prescribing of aliskiren.

Results: Of the 130 patients starting aliskiren, 94 (72%) received aliskiren in addition to ACEi/ARB, of whom 24 (26%) discontinued ACEi/ARB. So far, median duration of combined use in the remaining 70 patients was 270 (IQR 416) days. Mean systolic blood pressure was 168 ± 29 mmHg for starters, compared to 142 ± 19 for the non-aliskiren users. Starting aliskiren was positively associated with a higher number of previously used antihypertensive drugs, higher blood pressure and albumin/creatinin ratio, and lower HDL-cholesterol levels. Potassium level was recorded in the year before the start of aliskiren in 71 patients (54%), while in only 34% patients a level was recorded in the 4 months following initiation.

Conclusions: Aliskiren was predominantly prescribed in high-risk diabetes patients often on ACEi/ARB in Dutch primary care, while a trial on efficacy/safety of such combinations was still ongoing. Recommended monitoring of serum potassium was low.

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642. Changes in Antihypertensive Prescribing Patterns during 1990–2009

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Objectives: This study aimed to describe the use of antihypertensive medication in Extremadura (Spain) from 1990 to 2009 and its economic impact.

Methods: Information on antihypertensive drug (ATC C02, C03, C07, C08, C09) utilization was obtained from the community pharmacy sales figures reimbursed by the Health System of Extremadura (Spain). Data were expressed in defined daily dose (DDD) and DDD per 1,000 inhabitants per day (DHD).

Results: Antihypertensive consumption in Extremadura increased from 67.1 DHD in 1990 to 334.2 in 2009 representing a total increase in antihypertensive use of 80%. Agents Acting on the Renin-Angiotensin System (C09) were responsible for 44% of the total increase. Since 2007 the use of Angiotensin II antagonist has increased at the expense of ACE inhibitors (Table 1).

Table 1. Consumption of ACE inhibitors and Angiotensin II antagonist in 2009.

Group	ATC	DDD/1,000/day	Million euros
ACE inhibitors	C09A + C09B	84.9	6.0
Angiotensin II antagonist	C09C + C09D	102.9	29.7

Conclusions: The consumption of antihypertensive drugs in Extremadura has increased remarkably during the 20-year period of 1990–2009. In the last years the use of angiotensin II antagonists drugs appears to be having a significant economic impact.

643. Trends in Utilization of Medications with Adverse Metabolic Effects in a Managed Care Population between 1999 and 2008

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Background: Studies suggest thiazide diuretics (TD), statins (ST), beta-blockers (BB), atypical antipsychotics (AP), and antidepressants (AD) can impair glucose homeostasis. Little is known about concomitant use and its effects.

Objectives: To describe the concomitant utilization of these drug classes in a managed care population.

Methods: A time-series analysis was conducted in members aged 30–65 years in Kaiser Permanente Northwest (KPNW) between 1999 and 2008. Patients entered the study cohort at the date of first fasting plasma glucose (FPG) after six months of continuous enrollment (index date). Those with diabetes at index date were excluded (FPG≥126 or antihyperglycemic medication). Patients were followed for two years. Total person-years of exposure (PYE) were calculated by calendar year for each drug class: TD, ST, BB, AP and AD. Concomitant use was defined as overlapping exposure ≥1 day amongst classes, based on dispensing date and recorded prescription duration. Linear regression was used to analyze utilization trends over time.

Results: Mean age of the 106,255 members was 48 (Q1:43, Q3:55) years, 64.6% were female, and a total of 184,932 patient-years of follow-up were accrued. The most common combinations were BB/TD (2,747 PYE), BB/ST (2,248 PYE), and BB/AD (1,567 PYE). The most common three drug combination was BB/ST/TD (561 PYE). Between 1999–2008, the use of two drug combinations (11,059 PYE, mean = 5%, standard deviation (SD):0.2%, $p = 0.14$) and three drug combinations (1,767 PYE, mean = 0.1%, SD:0.01%, $p = 0.19$) did not significantly change. AD usage (mean: 10.5%, SD:0.4%, $p = 0.31$), ST usage (mean: 5.2%, SD:0.6%, $p = 0.67$) and TD usage (mean: 6.3%; SD:0.3%, $p = 0.18$) remained relatively constant, while BB usage decreased from 9.6% to 6.9% (SD:1.0%, $p < 0.01$), and AP usage increased from 0.2% to 0.7% (SD:0.1%, $p < 0.001$).

Conclusions: Use of AD, ST, and TZ remained constant, BB use decreased, and AP use increased. During the 10-year study period, concomitant use was stable over time at moderate rates. The potential for a synergistic effect of commitment therapy on glucose homeostasis warrants investigation.

644. Weight Loss Drug Consumption by the Brazilian Population Based on the POF 2002–2003

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Background: Brazil is one of the biggest consumers of drugs for weight loss treatment, according to previous publications. The use of these drugs without a medical superintendence can be very harmful to health, causing or aggravating cardiac diseases.

Objectives: This study aims to evaluate the consumptions of weight loss drugs by the Brazilian populations, based on data of the Household Budget Survey (HBS) 2002–2003 and also to know the profile of its consumers.

Methods: This analysis is accomplished with data from the Household Budget Survey (POF) 2002–2003, a cross-sectional study conducted by the Brazilian Institute of Geography and Statistics (IBGE) and held between May 2002 and May 2003. It involved interviews of a sample of 48.470 households. We performed a complex sample data

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analysis for the evaluation of the costs of the medicines used for weight loss. The data is stratified by gender and age of the buyer. The variables to be analyzed are: income, amount of expense deflated, gender, age, body mass index (BMI) of residents.

Results: 0.4% of the Brazilian population has used some kind of weight loss medications during the period of the study, with an average annual expense of US$ 161.19 per capita. Among women the annual average expenses were US$ 177.12 (95% confidence interval [CI] US$ 152.98, 201.32). Women spent more than men on average (US$ 177.15 annually for women and US$ 121.14 for men). The users are more likely to be women, 71,6% (95% CI 64.0, 78.1), young (69.4% under 45 years old) and only 20.9% were obese (95% CI 16.2, 26.7).

Conclusions: Most of the consumers of weight loss medicines in Brazil are not obese. We also noticed that the major consumers of these drugs are young women with normal weight or just overweight. The consequences of the use of this kind of drugs when not indicated (for obesity) may cause major health problems on the patients. So far, studies have showed that even when the weight loss medicines are indicated, the adverse effects can be very harmful to users.

645. Performance of Group Sequential Methods for Active Post-Licensure Medical Product Safety Surveillance Using Observational Health Care Databases

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Background: In order to improve post-licensure drug and vaccine safety surveillance, national systems that prospectively monitor observational health care data from large health plans have emerged, including the Vaccine Safety Datalink and Mini-Sentinel initiatives. Near-continuous sequential testing methods have been frequently proposed for use in such settings to facilitate rapid detection, while group sequential methods commonly used in randomized clinical trials (RCTs) have received less consideration.

Objectives: We propose a group sequential approach tailored for post-licensure safety endpoints and to account for complications like confounding that arise in this non-randomized setting and thus have not been previously examined in RCTs.

Methods: We compute sequential boundaries using Monte Carlo simulation and show how they can accommodate unequal between-test sample sizes and changes in confounder distributions among accruing subjects over time. We evaluate via simulation the performance of this approach across sequential designs suited for safety and not previously addressed by simulation studies evaluating RCT boundaries in efficacy contexts. Such designs include those with much higher frequency testing and designs that employ early conservatism followed by frequent testing. We apply this methodology to safety data on a new pediatric combination vaccine.

Results: Contrary to prior RCT simulations, we found major differences in the average time-to-signal detection and overall power between different group sequential designs.

Conclusions: Use of sequential methods to conduct surveillance for medical product safety using electronic health care data is challenging but has strong potential to provide a flexible and robust monitoring approach, as in RCTs.

646. Applying High Dimensional Propensity Score Method to the THIN Database with OMOP Common Data Model

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Background: The Observational Medical Outcome Partnership (OMOP) common data model (CDM) has been used to convert different US databases to a standard structure, so that different active surveillance methods developed and tested by OMOP can be directly applied. OMOP has assessed a reference set of 53 drug-outcome pairs (nine true positive drug-outcome pairs and 44 true negative controls) based on product labels, observational studies, and expert consensus. We have converted the Health Improvement Network (THIN) database to THE OMOP CDM.

Objectives: To test the high dimensional propensity score (HDPS) method applied to hypothesis generation on the THIN CDM and compare the results with the OMOP reference set. Methods: With THIN CDM, we directly used OMOP Drug Concept ID to define exposure and used the Condition Concept ID to define outcomes. With these definitions, we run OMOP HDPS SAS macro for all exposure-outcome pairs that had OMOP exposure-outcome associations with ''Ground truth'' as ''True positive risk'' or ''Negative control''. The propensity scores were calculated by using the automated program and the adjusted odds ratios were calculated by Mantel-Haenszel estimation, with stratified analysis of both 5 groups of propensity scores or 20 groups of propensity scores.

Methods: With the CDM THIN, we directly used OMOP concept ID to define covariates, exposure and outcomes. We run the OMOP HDPS SAS macro for all exposure-outcome pairs that had OMOP exposure-outcome associations with ''Ground truth'' as ''True positive risk'' or ''Negative control''. The propensity scores were calculated by using the automated program and the adjusted odds ratios were calculated by Mantel-Haenszel estimation,

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with stratified analysis of both 5 groups of propensity scores or 20 groups of propensity scores.

Results: With the THIN database in CDM, we were able to run the HDPS macro on 45 drug-outcome pairs out of the 53 pairs with "ground truth" defined by OMOP. Among the 8 pairs with "ground truth" being "true positive risk", the HDPS result shows that 6 pairs had adjusted odds ratio >1, of which four pairs had 95% lower confidence interval above 1 (Sensitivity 50%) . On the other hand, for the 37 pairs with "ground truth" being a "negative control", 28 pairs had lower confidence interval below 1 (Specificity 75.7%). When we changed the surveillance window ending date from the end of treatment to 30 days after starting date of treatment, the sensitivity became lower (from 50% to 28.6%) even thought the specificity is higher (from 75.7% to 97.2%).

Conclusions: With the THIN CDM, we could quickly apply the OMOP HDPS method and identify some drug-outcome pairs with "true positive risk", but the method as applied in this hypothesis generation framework did generate false positive results. Further improvement in performance could be anticipated with further experimentation of parameter choices.

647. Feasibility and Value of Creating Longitudinal Patient Records from Transcribed Clinical Notes

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Background: Clinicians commonly dictate clinical notes that are then transcribed into electronic text documents for patient medical records. However, this rich source of healthcare information is not available in common data sources for pharmacoepidemiologic research.

Objectives: To explore the feasibility and value of transcribed clinical notes and reports as a data source for pharmacoepidemiologic research.

Methods: A sample of transcribed progress notes from a cardiology practice in the United States was used as the data source. Natural language processing (NLP) methods were used to extract patient information (name, date of birth, and medical record number) from the note header, medical conditions from the problem list, and current medications. Patient information was used to link reports belonging to the same patient and information extracted from these reports became the patient's longitudinal record. Descriptive statistics including "age at most recent visit" for each patient were calculated. Sex of the patient was inferred from the use of titles (e.g., Mr., Mrs.) and pronouns (e.g., he, she) in the note. If sufficient evidence was not found in the note, the patient's sex was labeled "Unknown". Medical conditions extracted from problem lists were mapped to high-level disease areas.

Results: Of 3,028 documents were analyzed, resulting in identification of 2,335 patients (female = 36.53%, unknown sex = 11.95%, mean age = 66.45 SD 14.26). Over 4,300 distinct medical problems were identified, many with finer granularity than ICD9 codes and additional descriptors, quantifiers, and clinical inference (e.g., severe mitral regurgitation suggesting possible bioprosthetic value stenosis). The top 5 medical condition areas included hypertension (52%), dyslipidemia (27%), diabetes (22%), cardiac dysfunction (21%), and hyperlipidemia (21%). The top 5 medications included Aspirin (67%), Lisinopril (28%), fish oil (24%), Coumadin (23%), and Plavix (23%).

Conclusions: Transcribed clinical notes provide rich detail about a patient's health. Technologies like NLP and record linkage can be used to make a suitable data source out of this previously untapped resource.

648. Assessing Healthcare Data Linkage Capabilities Using an Online Database Resource

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Background: The scope of epidemiology research can be enhanced by linking different population datasets to allow broader analyses of diverse characteristics. It is important to be aware of the variety of data linkages that can occur.

Objectives: To determine the types of database (DB) linkages possible within or across various healthcare databases.

Methods: B.R.I.D.G.E. TO DATA® (www.bridgetodata.org), an online resource currently with 157 population healthcare DB profiles worldwide, was utilized to identify DBs with data linkage capabilities. A keyword search with "link" was conducted to identify various types of data linkages. An additional search using the criteria "Cross-sectional Population Databases" and keyword term "longitudinal" was conducted to identify DBs with records linked across survey periods. The two searches resulted in 111 unique DBs, 17 of which were excluded due to no data linkage capabilities. The remaining 94 DBs were reviewed for data linkage characteristics.

Results: The final set of 94 DBs had the following non-exclusive characteristics: 68 (72%) DBs directly linked to another DB, 19 (20%) had indirect linkage capabilities, and 28 (30%) were formed through DB linkages. The most common patterns included linkages to: health services DBs, e.g., prescription, diagnoses, and hospitalization data (56;60%); regional DBs, e.g., national registers (47;50%); vital statistics DBs (34;36%); or civil registries, e.g., government administrative DBs (33;35%). Some of the less common linkages were those by specific disease,

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survey, institution, practice type, or study cohort. Primary linkage methods were use of a unique ID or probabilistic matching. Data elements obtainable via linkage varied, but frequently included data on death, cancer, hospitalization, and prescriptions.

Conclusions: This study highlights a growing number of databases with data linkage capabilities. Specifically, 60% (94/157) of the profiles on www.bridgetodata.org describe data linkages. While many linkages exist, the most frequent are to regional or health services DBs; common data elements obtained are death and cancer data.

649. Using Database Enrollment To Exclude Subjects from Retrospective Studies

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Background: It is common in electronic database studies to define a study population by excluding subjects who lack a minimum duration of enrollment in the database after the index date (i.e., start of follow-up). This strategy simplifies analysis, but implications for validity are rarely discussed.

Objectives: To consider the validity of including people in retrospective studies based on completeness of follow-up.

Methods: Contrast retrospective methods with prospective study methods.

Results: In prospective studies, excluding subjects before the start of follow-up affects generalizability but not validity. Subjects with incomplete follow-up present a missing data problem. Excluding from analysis subjects with incomplete follow-up decreases precision but may be valid if subjects are missing at random. Otherwise, more sophisticated analytic methods are indicated to address bias due to informative censoring. In retrospective studies, the study population is selected after follow-up has been completed, and the distinction between excluding subjects before and after the start of follow-up is easily blurred. Nevertheless, analogous to a complete case analysis in a clinical trial, considering incomplete follow-up as an exclusion criterion in a retrospective study will be valid only if subjects are missing (i.e., exit the database) at random. This assumption has been termed implausible in prospective studies, and is no more plausible in database studies where reasons for exiting a database are typically unavailable. Resulting bias depends on the extent of missing data and the strength of associations with outcomes under study.

Conclusions: Excluding subjects with incomplete follow-up is appropriate only under narrow and unverifiable circumstances. Follow-up should start after all inclusion criteria are fulfilled, and subjects with incomplete follow up should be included in the analysis of retrospective database studies. As in prospective studies, we should quantify the number of subjects lost to follow-up and, if non-negligible, consider analytic methods appropriate for missing data in conducting sensitivity analyses that make assumptions explicit and quantify potential biases.

650. Use of Bayesian Method To Predict Missing Lifestyle Information in the General Practice Research Database (GPRD)

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Background: GPRD is an automated electronic medical records system with rich clinical information on lifestyle risk factors. However, there are significant numbers of patients in the GPRD that do not have any recorded lifestyle risk factor information. The degree of missingness could be random or attributed to its clinical significance during a particular physician encounter.

Objectives: Past studies demonstrated differential effects of dichotomous vs. categorical risk factor definitions on risk estimates. This study evaluated the use of the Bayesian approach (1) to address missing smoking exposure data and its impact on generalizability of baseline prevalence of these exposures; and (2) on risk estimates in univariate and multivariate Cox regression analyses.

Methods: Patients meeting enrollment criteria between 2003 and 2010 were selected for analysis. Information on smoking was obtained using related diagnosis codes or related information in the additional clinical detail (ACD) records. Missing smoking exposure data was estimated using a prior distribution of smoking exposure derived from patients with recorded information. Using Cox regression model, risk estimates for hypertension using Bayesian imputed and observed exposure information (model 1) were compared to smoking exposure defined as exposed/non-exposed/missing (model 2).

Results: Of 43.9% of patients in the study did not have any recorded smoking information. The Bayesian approach to impute missing smoking information increased the estimated prevalence rate of lifetime ever smoker from 36.5% to 63.0%. The estimated rate is comparable to published UK survey data. Such approach also had an effect on risk estimates (Model 1 crude hazard ratio [HR]: 1.57, 95% CI: 1.55–1.58 vs. Model 2 crude HR: 1.20, 95% CI: 1.19–1.22).

Conclusions: Two different approaches to define baseline smoking information had differential effects on risk estimates of hypertension. The use of the Bayesian Method to estimate missing lifestyle risk factors data appeared to create more generalizable prevalence rates in the GPRD. Future analyses are planned to find the minimum sample size need for a reliable probability function.

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651. A Clinical Classification Dictionary for Read Codes in the General Practice Research Database

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Background: The General Practice Research Database (GPRD) and The Health Improvement Network (THIN) UK electronic health records databases both use medical Read codes (RC). Combining RC into meaningful concepts and categories for defining outcomes and use in propensity score modeling as well as for safety signal detection, is useful; however an appropriate method for doing so is not well understood currently.

Objectives: To develop and evaluate a Clinical Classification Dictionary (CCD) to aggregate the RC for researchers using GPRD.

Methods: The five-character RC of the GPRD (Q1, 2011) were classified into three levels based on their first 1, 2 or 3 characters via a SAS program developed by the authors. We: (1) clinically reviewed the aggregated groups; (2) categorized them into three classes: diagnoses (Dx) usually starting with A to S, procedures (Px), and observations (Obx); and (3) marked the clinically informative categories commonly used in epidemiology studies. A 1:1 matched case–control study for patients with immune thrombocytopenic purpura (ITP) was used as an example to evaluate the automatically generated categories by the CCD as co-morbidities. We assessed the resultant code categories based on their prevalence, odds ratios, 95% CI, 2-sided statistical significance ($p < 0.05$), and clinical reviews. The SAS program automatically updates the CCD following each GPRD data release.

Results: Overall 83,751 RC were classified into: 30 level-1, 484 level-2 and 5164 level-3 categories. Only 50,316 RC were considered "clinically meaningful" on review: Dx (62%), Px (30%), and Obx (8%). Among the clinically informative concepts within the Dx, Px and Obx classes, there were 171, 29 and 14 unique level-2; and 1473, 309 and 415 unique level-3 groups, respectively. The study example identified 15 clinically important co-morbidities that were more prevalent ($p < 0.05$) in ITP patients vs. controls.

Conclusions: This semi-automated approach to meaningfully aggregating RC into the CCD generates a large pool of potentially important outcomes and covariates that is readily available for the design and analysis of epidemiology studies.

652. Development and Evaluation of Claims-Based Algorithms To Identify Advanced Chronic Kidney Disease

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Background: In administrative claims data, the stage-specific ICD-9 codes for chronic kidney disease (CKD) have been found to be insensitive in identifying CKD stages 3–5. There is a dearth of information on whether combinations of lab results with non-stage specific renal disease diagnosis or procedure codes can identify additional advanced CKD cases.

Objectives: To develop and evaluate coding algorithms to estimate prevalence of advanced CKD.

Methods: A base population was selected from a US healthcare claims database to include adults 18 + years of age with medical and pharmacy coverage for ≥12 months during 2006–2008. We identified advanced CKD (Stages 3–5) via three coding algorithms: (1) stage-specific CKD medical diagnoses (ICD-9) or procedures (CPT/HCPCS), or non-stage-specific renal disease diagnoses or procedures with laboratory results (GFR < 60mL/min/1.73m^2 or equivalent serum creatinine); (2) stage-specific medical diagnoses or procedures; and (3) only stage-specific medical diagnoses. Using each algorithm, we calculated crude prevalence of CKD with 95% CI (overall, by gender and age group) as well as age-gender standardized prevalence estimates (US Census 2000).

Results: The number and prevalence (95% CI) of advanced CKD using algorithm 1 (93,346, 0.54% [0.53–0.54%]), was much higher as compared to algorithms 2 and 3 (49,177, 0.28% [0.28–0.29%] and 48,473, 0.28% [0.28–0.28%], respectively). Using algorithm 1, we observed: (1) prevalence monotonically increased with age (0.1% vs. 3.1% for age groups 18–19 and 80 + years); (2) males had a higher prevalence than females (0.62% vs. 0.46%); and (3) among people aged 80 +, the prevalence (95% CI) was 3.9% (3.8–4.0%) for males vs. 2.5% (2.4–2.6%) for females. The age-gender standardized prevalence was 0.74% for algorithm 1 and 0.44% for both algorithms 2 and 3. Among the three algorithms used, algorithm 1 yielded results closest to expected rates, although still underestimating the prevalence of advanced CKD.

Conclusions: Identification of advanced CKD in claims databases is enhanced by supplementing stage-specific ICD-9 diagnosis codes and procedures with a combination of non-stage specific renal disease codes and lab data.

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653. A Novel Process for the Identification, Development and Assessment of Database Coding Algorithms for Seven Rheumatologic Conditions

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Background: A standardized process for identifying optimal coding algorithms for clinical events using diagnosis, procedure and treatment codes recorded in administrative claims is integral to conducting research that can lead to comparable results across studies.

Objectives: This study describes a method for defining high-quality coding algorithms for a set of seven rheumatologic clinical conditions.

Methods: We developed algorithms for seven rheumatologic conditions including acute gout (AG), ankylosing spondylitis (AS), fibromyalgia (F), lupus (L), osteoarthritis (OA), rheumatoid arthritis (RA), and systemic sclerosis (SS). We began with a literature review to identify coding algorithms that had been used in published studies. We also had a certified clinical coding expert independently recommend codes for inclusion. Codes identified from the literature or the coding expert were then reviewed by a general physician and a rheumatologist. Each physician was instructed to provide comments on the validity of each algorithm identified as well as recommendations to refine the algorithms.

Results: Across the seven rheumatologic conditions, 52 papers were retrieved for this study. Among these papers performance characteristics of the algorithms (sensitivity, specificity, positive predictive value, etc.) were provided in two studies for AG, 1 for AS, none for F or L, 1 for OA, 2 for RA, and 1 for SS. In an effort to determine how well these final clinical algorithms assessed the prevalence of the selected rheumatologic conditions, the authors applied the clinical ICD-9 coding criteria to a full medical claims database (MarketScan® from Thomson Reuters) and compared the prevalence to NHANES data (for all clinical conditions available in that survey). Full results for each coding algorithm and prevalence estimates will be presented.

Conclusions: This approach used the most recent peer-reviewed literature and coupled it with expert insight from ICD-9 reimbursement, clinical and epidemiological expertise. The result is an evidence-based preferred list of coding algorithms for seven rheumatologic conditions for use in conducting research using administrative claims data.

654. Developing Quality Scores for Electronic Health Records for Clinical Research

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Background: The aims of this study are to investigate data quality in the General Practice Research Database (GPRD) and to develop a framework for characterising data quality over time.

Objectives: These aims will be implemented by constructing quality scores for each practice and using these scores in a visualisation toolkit whereby users can interactively select practices based on two criteria: (1) quality; and (2) suitability of the patient base for the intended study.

Methods: Using records from all 629 practices contributing data to the GPRD each year between 2000 and 2010, we investigated basic and intermediate measures related to data quality, including missing values in table columns, recording of lifestyle measures, specificity of Read codes for disease areas and recording related to specific diseases. The distributions of these practice-based variables and the correlations between them were investigated using summary statistics, graphs and correlation analysis.

Results: Recording of most measures significantly improved between 2001 and 2010. This was particularly noticeable for Quality and Outcomes Framework (QOF) incentivised recordings. Many of the measures were reasonably well-recorded by most practices. However there were large variations between practices and nearly all variables had very skewed distributions, with several outliers (representing practices who performed far less well). Correlations between variables in the same categories of measures were often quite high, but correlations between variables representing different categories of measures were generally very weak, and practices who were poor at recording one measure were often good at recording all others.

Conclusions: The quality of records has steadily improved since 2000 for most measures – particularly those for diseases and tests that are QOF incentivised. However, the lack of intercorrelations between variables for different types of measures, suggests that characterising each practices by one or two overall quality scores for each practice may not be feasible. A better approach may be to develop scores based on the disease area of interest.

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655. A Comparison of Drug Exposure Characteristics across a Range of Drugs and Databases

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Background: Administrative Claims (Claims) and Electronic Health Records (EHR) contain records of patient drug exposures but recorded values vary by database. When used for analysis, exposure length is derived by different methods depending on available values. The use of a Common Data Model (CDM) enables comparison of derived exposure characteristics across disparate databases.

Objectives: To compare characteristics across a variety of drug exposures in a Claims ? an EHR database that have been transformed into a CDM using standard approaches for deriving exposure length.

Methods: Claims EHR source data were transformed into a CDM. Exposure length was calculated using days supply available in Claims and derived using the most common days supply for a product/strength combination for EHR. A variety of acute ? chronic drugs were analyzed. Exposed patients between ages 18–65 with at least 1 year of eligibility after exposure were selected and all drug exposures examined. Analysis for each drug/database was performed twice – first without bridging treatment gaps then bridging gaps of 30 days or less. The avg. number of exposures per patient (EPP) avg. exposure length (EL) were calculated compared.

Results: With no treatment bridging, avg. EPP was 2.04 times greater in Claims (3.9 Claims, 1.9 EHR). The difference was largest for chronic drugs (4.7 Claims, 2.1 EHR). Avg. EL was 2.8 times longer in EHR (148 vs. 53 days), with acute drugs exhibiting the largest disparity (123 vs. 30 days). With treatment bridging differences were less pronounced. Avg. EPP was still greater in Claims but the difference was smaller (1.9 Claims, 1.7 EHR). Overall avg. EL was 1.1 times longer in EHR (169 vs. 153 days) but shorter for chronic drugs in EHR (185 vs. 235 days). The impact of bridging was most significant on Claims. The avg. EPP decreased by 50% for Claims vs. 10% for EHR. The avg. EL was 2.9 times longer after bridging in Claims vs. 1.15 times in EHR.

Conclusions: Characteristics of drug exposure can vary depending on database and approach used for deriving exposure length. Use of a CDM can support rapid comparison of data characteristics such as derived exposure length among disparate databases.

656. Examination of the Completeness of Hospitalization Data from the MedMining Electronic Medical Record (EMR) Database

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Background: One of the key challenges in utilizing a medical database to conduct pharmacoepidemiology research is the completeness of the data for the exposures and outcomes under study. An EMR database can provide tremendous detail on patients, their clinical conditions, and their drug exposures, but the completeness of the ascertainment of clinical outcomes, particularly in regards to hospitalizations, is often unknown.

Objectives: To determine the completeness of ascertainment of hospitalized gastrointestinal (GI) bleeding events in patients enrolled in a managed care plan and included in a large EMR database.

Methods: A large EMR database from MedMining was the source of data to examine the completeness of GI bleeding events for the time period studied (January 2009–January 2011). We examined patients who were enrolled in the associated health plan and had full medical claims linked to all GI bleeding hospitalizations. The medical claims were considered the gold standard (since they would include all covered medical expenses) and were compared to the EMR system to determine how many of the total hospitalized GI bleed events were identifiable in the EMR database as well (since the EMR database did not include all hospitals in the potential catchment area).

Results: Of the 1,148 patients were identified who had both EMR and medical claims data available during the time of a GI bleed hospitalization event. Of the 1,148 patients, only 11.7% of the GI bleed hospitalizations were identifiable in the medical claims data but not in the EMR database.

Conclusions: Over 88% of the GI bleed hospitalizations identified via medical claims were identifiable using the EMR database alone. It appears that the EMR database alone is sufficient in identifying the vast majority of serious hospitalization events, such as GI bleeds.

657. Back in Barcelona, the Landscape of Database Research over the Last Decade

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Background: Databases (DBs) are a cornerstone of pharmacoepidemiology research. Little research has been done on their use.

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Objectives: Quantify the contribution to pharmacoepidemiology of studies conducted in automated health care DBs over the last decade through abstracts accepted at ICPE in 2000 (Barcelona) and 2011 (Chicago).

Methods: We reviewed abstracts from the PDS supplements for both conferences to identify studies of drug utilization, safety endpoint (s), validation, and disease epidemiology in populations covered by DBs. A DB was defined as electronic medical or administrative health records for populations with individual, longitudinal person-level data. We abstracted data on author names, affiliations and country; study goal; number of DBs in the study; and DB name (s), country, and world region. We consulted literature and contacted authors for key missing information. We tabulated the DB abstracts by country and report the number of studies by country, world region, collaborative studies across countries, and other key findings.

Results: Abstracts doubled from 389 in 2000 to 806 in 2011. DB abstracts contributed 38% in 2000 and 45% in 2011. The most common study goal was drug utilization in 2000 and safety endpoints in 2011. Abstracts on validation increased from 0 to 20, the number of multi-DB abstracts doubled from 6% to 12%, and the number of countries covered increased from 14 to 22. The increase in covered countries in 2011 was primarily from Europe (mostly the Nordic countries: Norway, Finland, and Iceland) and the Asian Pacific Region (Taiwan and Japan). In 2000, the UK, USA, and the Netherlands contributed the largest number of abstracts (more than 10 each); in 2011, the USA, UK, Netherlands, Denmark, Taiwan and Canada contributed the most (more than 20 each). The world region with the largest growth was the Asian Pacific with five abstracts in 2000 and 33 in 2011.

Conclusions: Over the last decade there has been a remarkable expansion in the number of countries in which pharmacoepidemiology research can be conducted in DBs. Studies across DBs, once infrequent, have become common and include collaborations across countries.

658. The CODEX Method: A Systematic Approach for Harmonization of Event Measurement and Data Extraction for Multi-Database Studies

An Application in the SOS Project René Schade,[1] Juliane Neubronner,[2] Tania Schink,[2] Vera E Valkhoff,[1] Silvana Romio,[1] Andrea Arfè,[3] Jordi Castellsagué,[4] Giovanni Corrao,[3] Ron Herings,[5] Silvia Lucchi,[6] Gino Picelli,[7] Huub Straatman,[5] Frantz Thiessard,[8] Cristina Varas Lorenzo,[4] Marco Villa,[6] Edeltraut Garbe,[2] Miriam CJM Sturkenboom.[1] *[1]Erasmus University Medical Center, Rotterdam, Netherlands; [2]University of Bremen, Bremen, Germany; [3]University Milano-Bicocca, Milan, Italy; [4]RTI Health Solutions, Barcelona, Spain; [5]PHARMO Institute, Utrecht, Netherlands; [6]Local Health Authority ASL Cremona, Cremona, Italy; [7]International Pharmaco-epidemiology and Pharmaco-economics Research Center, Desio, Italy; [8]University Bordeaux Segalen, Bordeaux, France.*

Background: Harmonization of event measurement and data extraction are important steps before performing statistical analyses in multi-database studies. In the European Commission-funded SOS project, seven databases (DBs) from four European countries were combined to study the risk of cardio-/cerebrovascular and gastrointestinal events with NSAID use to develop decision models for clinicians and regulators. Among DBs, four different terminologies were used to code events (ICD-9,ICD-10,READ,ICPC) which challenged event measurement harmonization.

Objectives: To develop a systematic approach (referred to as the CODEX method) for harmonization of event measurement and data extraction. To facilitate work flow and prevent event misclassification.

Methods: We used the Unified Medical Language System (UMLS) to integrate lists of truncated codes from four terminologies for specific medical concepts (terminology mapping). We developed the CODEX method to systematically centralize procedures for management, review, and distribution of codes. Developments included the CODEX software to match database-specific exact codes to truncated UMLS codes. Physicians reviewed the lists of exact codes according to specific event definitions.

Results: Our terminology mapping provided lists of truncated codes for medical concepts which were comprehensive, yet not complete for all event definitions. The review of matched exact codes showed that, in several cases, some codes were not in line with specific event definitions, e.g., for specific cardio-/cerebrovascular and gastrointestinal outcomes. Systematic centralization with the CODEX method allowed for prevention of errors which were identified with prior decentralized (local) code management strategies.

Conclusions: The CODEX method provided consistency, facilitation, and documentation for harmonization of event measurement by applying a systematic approach for code management. It filled a conceptual and logistical gap between a central UMLS-based terminology mapping and local data extractions. The method allows for efficient prevention of event misclassification in multi-database studies.

659. Use of Common Data Model To Enable Meaningful Comparison of Disease Burden among Disparate Databases

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Background: Use of a Common Data Model (CDM) to standardize underlying data assumptions and format

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enables consistency in the application of research methods and production of meaningfully comparable results across disparate data sources.

Objectives: This study compared the baseline disease burden, as measured via a standard method deriving Charlson Comorbidity Index (CCI), which was applied to multiple observational databases after all source data was transformed into a standard CDM format.

Methods: Two unique patient cohorts, (1) newly diagnosed and treated depression patients (DEP); and (2) newly diagnosed rheumatoid arthritis patients (RA) were identified using equivalent definitions from multiple claims databases which had been previously transformed into a standard CDM format. CCI was calculated for each Cohort using a single SAS macro developed for CCI derivation using CDM-format data Descriptive information on CCI, in aggregate and stratified by age category and gender, was compared separately for the DEP and RA cohorts across all databases.

Results: Despite a common data format, consistent cohort definitions, and a single method for CCI derivation, the calculated CCI varied by as much as 20% (RA) and 50% (DEP) across the different databases used for this study. Gender had little influence on CCI differential. CCI differential generally decreased with advancing age category for both DEP and RA, with largest differentials exceeding fourfold in 18–30 age group (DEP) and smallest differentials of 10% in 80+ age group (DEP).

Conclusions: Common Data Models provide an efficient way of enabling meaningful comparisons across disparate data sources. Disparities in CCI results, despite identical cohort definitions and the application of a single SAS macro, are likely the result of differences in underlying populations, data capture process, and/or functional ability and/or incentive to record complete information in source data. Future research should focus on how each of these factors may impact disease burden indices.

660. Potential Bias When Excluding Concepts from Terminologies with Different Granularity: An illustration in the SOS Project

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Background: The SOS Project aims to assess the risk of cardiovascular and gastrointestinal events of non-steroidal anti-inflammatory drugs. Seven European databases (DB), which contain health records of more than 35 million citizens, are involved in the project. These DB use four different terminologies to code events (ICD-9-CM, ICD-10-GM, READ and ICPC).

Objectives: To quantify the cases where a bias due to the exclusion of concepts appears in real DBs involving different terminologies.

Methods: We used the Unified Medical Language System (UMLS) which is an integration system handling more than 150 terminologies as a starting point for harmonization of event measurements. Using the UMLS, we constituted a list of concepts and all their descendants in the four terminologies involved in the project. Because the terminologies have different granularities and that it was decided to exclude concepts -for example when a specified cause was not related to a drug- we were faced with a new theoretical heterogeneity if the excluded concept was not present in each hierarchy of the involved terminologies.We compared the initially extracted concepts with the finally retained concepts after code review by DB holders and clinicians.

Results: Fourteen diagnosis outcomes and 59 covariates were identified in the SOS project corresponding to 11,076 different UMLS concepts from which 1,939 concepts were excluded after code review. For 149 out of the 1,939 excluded concepts, this could only be done in the finer granular terminologies and not in the coarser granular terminologies such as ICPC and/or ICD-9.

Conclusions: Although the UMLS can be used to map terminologies, the differences in granularity in EU based DB poses extra difficulties upon code review. Strategies could be (1) excluding the concept and its descendants (exclusions will not be done in certain terminologies only); (2) excluding the parent of the initial excluded concept, and all its descendants (some records that should have been kept will be ignored); (3) avoiding any exclusion (some patients will be wrongly selected). Future research should investigate the impact of these choices.

661. Using Advanced Healthcare Data Analytics To Identify and Characterize Central Venous Catheterization Episodes Via Electronic Health Records in the Veterans Affairs

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Background: Observational healthcare data are often used to study patient populations and outcomes of interest.

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Electronic Health Record (EHR) data provide a granular and longitudinal look at patient care; however, much information is buried within the narrative text of clinical notes and is not typically available for research.

Diagnosis and procedure codes pose two difficulties when identifying central venous catheter (CVC) episodes: (1) they are underused; and (2) they are associated with the encounter and not the actual CVC event.

Objectives: Our objective was to use Natural Language Processing (NLP) to accurately identify patients with an inpatient CVC episode in a large, population-based database.

Methods: We applied advanced healthcare data analytics with natural language processing (NLP) to extract meaningful information about patient care from text clinical information in the Veteran Affairs nationwide EHR database. The NLP was designed to help identify and characterize CVC episodes for patients with an inpatient encounter. Patients were characterized as having (1) a billing code for catheter insertion; and (2) having had a chest X-ray during an inpatient encounter where the presence of a CVC was identified by NLP.

Results: 1.2M patients with an inpatient encounter were found in the VA between 1/1/2006-12/31/2010. Of them, 54,676 patients were identified as having at least one inpatient CVC episode using billing codes. Of 119,768 additional patients were preliminarily identified via NLP, resulting in a total of 174,444 CVC patients.

Conclusions: Fivteen percent of inpatients had a CVC placed and 69% of CVC patients were only identified via NLP. These rates are consistent with previously published literature. This work shows that NLP provides an effective way to leverage rich observational data. We will use this to study health outcomes in relation to the catheter placement and related interventions.

662. Example of Introduction of Database in Pharmacovigilance Department Practice

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Background: Crimea is leading regions in Ukraine in registration of adverse reactions (ADR). Amount of reports in region is about 1,100/year. The analysis of them without use of database took 4 weeks and involved five workers of department. The regular checking of information requested by other institutions and detailed analysis of it, storage of reports, system of accounting, personal data protection were also a problem.

Objectives: The main aim of the work was development and introduction of database in practical work of the pharmacovigilance (PV) department.

Methods: We have developed own database – ARCADe (Adverse Reactions in Crimea Autonomy DatabasE) based on commercial software of FileMaker Inc. The reasons to choose it were affordability, accessibility, simplicity (graphical multilanguage interface), built-in statistical functions, support system, cross-platformity, multiuser password protected access, ability to import/export data, search module and ability to build web-interface.

Results: ARCADe has modules for work with ADR reports, ICD-10, ATC-DDD index, address-book and drug reference system. Database allows the check-up of data (codes and information about hospitals, manufacturers, authorization dates, doses and forms). We use algorithms for search of interactions, polypharmacia cases, cases of allergy ignoring, search of duplicates of reports. In 2011 we found 22 copies (2.1%) in 1067 sent reports. The annual analysis took 5 hours and involved one worker of our department. Average time for creation of one record in ARCADe took 5 minutes. ARCADe allows to analyze data by new parameters, i.e., analysis by date, PV activity in institution.

Conclusions: Use of local databases for recording, storage and analysis of high-volume multiparameter ADR information is economically sound approach in PV. FileMaker based system is easy for handling and opens new perspectives for analysis. It may be easily broaden for other departments because needs only installed FileMaker software and file of empty database. It also has perspectives for further development (intranet and web systems).

663. Utility of Pharmacovigilance Reports for LQT/TdP Case Ascertainment

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Background: Drug-induced long-QT syndrome (LQTS), Torsades de Pointes (TdP) and Ventricular Fibrillation (VF) are rare but potentially fatal conditions that have led to a number of postmarketing withdrawals in recent years, with an annual incidence of surviving cases around 1 in 100,000 per adult population.

Objectives: Anonymised MHRA pharmacovigilance reports were explored for utility of case ascertainment for studies of severe QTc prolongation, TdP and VF as part of the FP7 ARITMO collaboration (Arrhythmogenic potential of drugs, HEALTH-241679). Sensitivity, specificity and PPV for LQT, TdP and VF will be prospectively evaluated.

Methods: Anonymised MHRA reports with details of drug usage and symptoms were searched from 2000 to 2010 using standardised MedDRA queries (SMQs) and text searches for adult surviving cases of drug induced LQTS, TdP and VF (across all drugs). Statistical analyses were carried out with SPSS version 17.0.

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Results: One hundred and sixty one adult cases of LQTS, TdP and VF were ascertained. Prolonged QT was most frequently reported (65.8%, n = 106) $p < 0.001$; compared to TdP (12.4%, n = 20), VF cardiac arrest (12.4%, n = 20), and VF (9.3%, n = 15). The mean age of prolonged QT cases was 59.0 [22.4] year; TdP 61.9 [18.4] year; VF cardiac arrest cases 60.8 [15.0] year and VF 59.7 [17.8] year. Overall there were 108 (67.1%) female cases ($p < 0.01$). By category: 70.8% of Prolonged QT cases were female (n = 75); 80% of TdP (n = 16); with 50% VF cardiac arrest (n = 10) and 47% of VF (n = 7) cases. The mean age of all reported cases was 59.7 [20.6] year. The mean age of females at the time of the ADR report was 61.9 [19.9] year, compared to males whose mean age was 54.8 [21.8] year; however this was not significant. Pilot studies estimate ascertainment rates using pharmacovigilance reports as approximately 10–15% and PPV 20–50%.

Conclusions: Females were significantly more likely to be reported as LQT/TdP ($p < 0.01$), although there was no statistical difference in ages between men and women with reports of LQT/TdP. The most frequently reported diagnosis was "Prolonged QT"($p < 0.01$). Although there are several potential cases eligible for recruitment into LQT/TdP studies; pilot studies show that ascertainment rates are likely to be modest.

664. An Electronic Causality Assessment Tool for Drug-Induced Liver Injury

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Background: Drug-induced liver injury (DILI) is the leading cause of acute liver failure in the US. Detecting DILI is challenging due to its low incidence, lack of diagnostic markers and its idiosyncratic nature.

Objectives: Develop an electronic algorithm to detect DILI cases based on the Roussel Uclaf Causality Assessment Method (RUCAM) and test it in an electronic medical record (EMR) on patients receiving medications associated with hepatotoxicity.

Methods: We undertook a retrospective cohort study at Kaiser Permanente Southern California. Study participants were ≥18 years old with 12 months of continuous membership plus drug benefit prior to exposure to one of 14 drugs commonly associated with DILI events. Patients with a new order for at least one of the study medications between January 1, 2003 and August 31, 2011 were eligible for inclusion. The electronic algorithm covered seven areas of causality: (1) Time to onset; (2) Course; (3) Risk Factors; (4) Concomitant Drugs; (5) Non-Drug Causes; (6) Prior Hepatotoxicity Information; and (7) Re-challenge. Operational definitions were developed in collaboration with the Observational Medical Outcomes Partnership and DILI experts, and programmed into the electronic algorithm – an eRUCAM. Cases were categorized based on causal evidence into five categories ranging from "Highly Probable" to "Excluded". Rates of DILI events per 10,000 exposures were calculated.

Results: We identified 14,925 potential DILI events following 3,321,835 study drug exposures. The most common type of liver injury was cholestatic 65.0% followed by hepatocellular 29.4% and mixed 5.6%. DILI events were categorized as either probable or highly probable in 15.5% of cases, 59.6% were identified as possible and 24.9% were listed as unlikely or excluded. The overall rate of DILI events was 45 events per 10,000 exposures while the rate of probable or highly probable DILI events was 6.9 per 10,000 exposures.

Conclusions: An electronic causality assessment algorithm was developed and successfully applied to EMR data. Validation of the eRUCAM is needed comparing these results with the "gold standard" medical record review by DILI experts.

665. Assessment of a Severity Classification Approach to Detecting Signals of Severe Drug Induced Liver Injury (DILI)

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Background: Severe DILI is a major safety concern in pharmacovigilance. It is beneficial to develop a robust method for early detection of hepatic signals.

Objectives: To assess the performance of a severity classification approach for relevant Preferred Terms (PTs) in detecting signals of severe DILI.

Methods: We assessed a method using PTs listed in MedDRA's Hepatic Standardized Queries and other relevant PTs, such as coma. These PTs were grouped into three categories based on severity of liver injury (A-severe, B-non-severe, C-severity not specified). The disproportionality of these categories was then analyzed using the FDA's Adverse Event Reporting System (AERS) based on empirical Bayesian geometrical mean (EBGM). A lower bound of 90% confidence interval of EBGM (EB05) >2 for category A in two continuous quarters was used to define a signal of severe DILI. Selected drugs with known hepatotoxicity (i.e., troglitazone, propylthiouracil, nefazodone, and bosentan) and drugs without known hepatotoxicity (i.e., statins, heparin, and venlafaxine) were used. For drugs with known hepatotoxicity, the time to signal detection was compared to that of initiation of regulatory action due to DILI (withdrawal or boxed warning).

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Results: Our method detected signals of severe hepatotoxicity for troglitazone and propylthiouracil 2–5 years earlier than the time of initiation of regulatory action. No signal of severe hepatotoxicity was detected for bosentan which was launched with a hepatic boxed warning and nefazodone which was labeled with a hepatic boxed warning in 2002. Nevertheless, signals indicating non-severe and/or non-specific hepatotoxicity were detected for bosentan since launch and for nefazodone since 2005. For all nine drugs without known hepatotoxicity, no severe hepatotoxicity signal was detected.

Conclusions: The results indicate that a method based on severity classification is useful in early detection of severe hepatotoxicity and can add value to routine pharmacovigilance. Nevertheless, further studies are needed to evaluate its effectiveness.

666. Prevalence and Characterization of Potential PPI-Clopidogrel Interaction in a Prescription Database in 2006–2009

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Background: Recent studies discovered a potential risk for adverse cardiovascular events associated with the dual use of clopidogrel and omeprazole/esomeprazole. FDA and EMA have recently discouraged the combined use of these agents unless strongly indicated.

Objectives: The aim of this study was to assess the annual prevalence of these potential drug-drug interactions (pDDIs) in Campania, an Italian Region of almost 5.5 million inhabitants, from January 2006 to December 2009.

Methods: We conducted a retrospective cohort study on the 2006–2009 Campania outpatient pharmacy databases of residents, aged 6–95 years. Based on the ATC classification system, prescriptions of the two proton pump inhibitors and clopidogrel were retrieved for the analysis.

Results: Omeprazole users were 185,883 (3.4% of all residents) in 2006, to 422,811 (7.8%) in 2009; esomeprazole users were 181,620 (3.3%) in 2006, to 69,858 (1.3%) in 2009; clopidogrel users were 8,750 (0.2%) in 2006, to 11,893 (0.2%) in 2009. 37.9/100,000 residents were exposed to at least one concomitant prescription of omeprazole-clopidogrel in 2006; this rate showed a trend towards an increase, up to 57.7/100,000 residents in 2009. 25.4/100,000 residents were exposed to at least one concomitant prescription of esomeprazole-clopidogrel in 2006; this rate showed a decreasing trend, with 8.8/100,000 residents in 2009. Marketing of generic omeprazole probably accounted for these different temporal patterns. As about one out four patients with clopidogrel received also a prescription of omeprazole/esomeprazole, anagraphical characteristics of concomitant cohorts are quite similar to those of clopidogrel cohorts (70% men, mean age 66 years). 70–80% of patients with concomitant events of both pDDIs received prescription of interacting drugs in the same day (co-prescriptions).

Conclusions: In 2009, out of almost 12,000 Campanian patients treated with clopidogrel, 3,600 were exposed to over 16,000 concomitant prescriptions of omeprazole/esomeprazole, with a potential increased risk of cardiovascular outcomes.

667. The EU-ADR Alliance: A Federated Collaborative Framework for Drug Safety Studies

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Background: EU-ADR is a European research project resulting in a computerized system exploiting data from electronic healthcare records (EHR) for early detection of adverse drug reactions. The system identifies drug-event associations from epidemiological data and uses computational and text mining techniques to substantiate them in the light of current biomedical knowledge. EHRs of +30 million patients from several European countries are available. The EU-ADR system has been initially built for addressing relevant events for drug safety surveillance such as upper gastrointestinal bleeding, anaphylactic

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shock, acute renal failure, rhabdomyolysis, myocardial infarction, etc.

Objectives: Based on the resulting system, the EU-ADR Alliance is devised as a collaboration framework for running studies and answering drug safety questions in a federated manner, using extracted data from multiple European private and public EHR databases.

Methods: The EU-ADR Alliance will be composed by members bringing in relevant expertise (EHR databases, information technologies). It is based on the concept of federated databases, non-competition with its members, independence and scientific interest. It will undertake commissioned or members individual studies and the annual Alliance Research Plan. The advantage of running studies through the Alliance is that more powerful studies can be set up and run faster, given that a governance structure and working methods are in place.

Results: EU-ADR Alliance candidate member organisations include eight European EHR database with access to +45 million patients from Italy, Netherlands, UK, Germany and Denmark. A proof of concept phase is ongoing. Studies contracted by the European Medicines Agency will utilise the EU-ADR Alliance concept and operations. These studies concern the patterns of use of oral contraceptives; exploring an association between cardiac valve disorders and the use of biphosphonates and the monitoring of the effectiveness of risk minimisation in patients treated with pioglitazone-containing products.

Conclusions: The EU-ADR Alliance will provide an unprecedented framework to run drug safety studies across EHR databases with important power and speed benefits.

668. Fragile Skin? From Sensation to Evaluation

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Background: "Fragile skin" is a subjective (experienced) and objective (clinically evaluated) perception of the skin's condition. "Fragile" skin is based on constitutional factors concerning the structure and function of the epidermal "barrier" (although any disturbance of this structural barrier inevitably leads to elicitation of inflammatory reaction). It can thus be defined as a constitutional lower resistance threshold to minor environmental aggressions. Just like a baby's skin, "fragile" skin is delicate and requires special skin care which would allow strengthening of skin's natural protective qualities.

Objectives: The aim of this work was to evaluate the subjective perception of "fragile skin", i.e., to see whether the notion of "fragile skin" has a precise connotation with adult subjects from four different countries with diverging cultural, ethnical and geographical background: France, Spain, Sweden and Japan

Methods: In each of the four countries, a sample representative of the overall adult population was prepared by the CSA Santé. A series of questions were asked, including: "Do you think that you have fragile skin?" A total of 4,500 subjects were questioned.

Results: At the Question: "Do you have fragile skin": 29% of French, 34% of Spanish, 25% of Swedish and 52% of Japanese respondents answered "yes". It was therefore observed that approximately one-third of the European population considered their skin to be fragile, while for Japan it was one in two persons. Trends according to gender were identical in all countries, with women consistently higher in number to express the sentiment of having fragile skin: 39% in France, 33% in Spain, 28% in Sweden and 59% in Japan

Conclusions: This evaluation of representative populations provides a series of unprecedented responses in terms of subjective perception of fragile skin. These results now need to be confirmed by objective evaluation on the basis of relevant and specific tests. The nature of the correlation between the dermatosis and the propensity to claim to have fragile skin also needs to be specified. The notion of fragile skin is evidently a part of the personal experience of a non negligible portion of any given country's population addressed in this study.

669. Drug Screening Tests Improve Treatment Retention in a Cohort of Outpatients Starting Opioid Substitution Therapy

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Background: According to French guidelines concerning opioid substitution treatment (OST), drug screening tests are recommended for the follow-up of opioid-dependent patients. However, their value in ambulatory practice has not been studied.

Objectives: To assess the value of drug tests in the therapeutic management of opioid-addicted patients in an outpatient setting.

Methods: A retrospective cohort was built from the January 2009 to June 2011 data of the French health insurance system database for the Midi-Pyrenees region. Patients starting opioid substitution treatment, defined as patients with no reimbursement for an opioid substitute during the previous 6 months, were included from July 2009 and followed for 12–24 months. Two groups of patients were

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defined: the drug test group (at least one drug test reimbursement) and a control group (no drug test reimbursement). The primary outcome measure was OST retention. Statistical analysis used a Cox model adjusted for potential confounding factors. Drug test exposure was modeled as a time-dependent variable with a single change.

Results: The cohort included 1,507 patients (median age 32 ± 13 years, 75% men) of whom 72% received buprenorphine and 28% methadone. Median OST retention was 91 days (3 months). The 6-month retention rate was 35.3% (95% CI: 32.9%–37.8%). During follow-up, 36 subjects (2.4%) had at least one drug test reimbursement. Median treatment retention was 88 days in the control group and 243 days in the drug test group ($p < 0.001$). With a multivariate Cox model, a drug test was a protective factor for treatment retention with a relative risk of 0.37 (95% CI: 0.21–0.65).

Conclusions: Use of a drug screening test in follow-up of opioid substitution treatment, although rarely prescribed, significantly improved treatment retention.

670. Abstract withdrawn by author.

671. Baseline Burden of Heart Failure Limits Benefit of ICD for Elderly Recipients

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Background: Survival benefit after Implantable Cardioverter Defibrillator (ICD) implantation for primary prevention (primary ICD) may differ between trial populations and elderly recipients.

Objectives: To assess survival after primary ICD in relation to the impact of baseline heart failure (HF) burden.

Methods: Linking data from the CMS ICD registry and the Medicare files (05–08), we identified primary ICD recipients ≥66 years with ejection fraction ≤35%. Prior HF hospitalizations and length of current hospitalization prior to implantation were used to define HF burden. All cause mortality curves, estimated crude mortality and adjusted hazard ratios (HRs) were constructed using proportional hazards regression.

Results: Of 66,974 ICD recipients (73% male, 88% white, mean age 75), 11,876 (18%) died during a mean follow-up of 1.4 years (3-year mortality 31%, which was higher than that in major primary ICD trials). The number of prior HF hospitalizations and length of hospitalization prior to implantation each predicted shorter survival post-ICD. Mortality at 3-year was 60% for recipients with ≥3 prior HF hospitalizations, vs. 27% in patients without prior HF hospitalizations (adj. HR 3.3). Mortality at 3-year was 25% in patients who received ICD on admission day vs. 52% in those with >1-week hospitalization prior to implantation (adj. HR: 3.2). From the number of prior HF hospitalizations and length of hospitalization prior to implantation, we defined four levels of HF burden that showed distinct post-implantation survival. Mortality at 3 years ranged from 21% in the half of patients with low HF burden to 63% among 1,661 patients with the highest burden. Median survival in high and very high HF burden patients was three and 1.7 years, respectively.

Conclusions: Nearly one third of elderly ICD recipients died by three years, limiting the survival benefit and cost-effectiveness that derive from trial populations. However, those patients with low HF burden (no prior hospitalization who received ICDs on the admission day) had similar survival to the younger subjects in trials. Pre-existing chronic and acute HF burdens should be considered when anticipating benefit from primary ICDs in elderly patients.

672. Effect of Physician and Hospital Experience on Outcomes Following Carotid Artery Stenting (CAS)

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Background: Physician and hospital experience may alter outcomes following CAS.

Objectives: To quantify the effect of physician and hospital experience on outcomes following CAS in Medicare patients.

Methods: We identified Medicare beneficiaries ≥66 years undergoing CAS between 2005 and 2009. We quantified the association between (1) past-year CAS volume; and (2) annualized CAS volume (if length of CAS experience ≥6 months) on 30-day mortality and length of index hospital stay (LOS) at the physician- and hospital-level, using modified Poisson regression (mortality) and linear regression (LOS) adjusting for age, gender, and race, and testing for trends across experience levels.

Results: Crude 30-day mortality risk was 1.9% (95% CI: 1.7–2.0) and mean LOS was 2.7 ± 4.3 (range: 0–92) among 33,108 CAS procedures performed by 2,815 physicians. Median past-year and annualized CAS volume was 7 (Interquartile Range [IQR]: 3–17) and 12 (IQR: 6–22), respectively. There was a significant downward trend ($p < 0.0001$) in crude 30-day mortality with increasing past-year CAS physician volume; 2.6% for zero; 2.1% for

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1–4; 2.0% for 5–9; 1.6% for 10–19; 1.4% for 20–24; and 1.3% for ≥25 past-year CAS volume. Relative to patients treated by physicians with no past-year CAS experience, adjusted 30-day mortality risk was 0.5 (95% CI: 0.3–0.7) for physicians performing ≥25 CAS. Greater CAS hospital volume was also associated with lower mortality. Crude 30-day mortality risk was 2.4% for institutions performing < 10 past-year CAS; 2.0% for 10–19; 1.8% for 20–39; and 1.3% for ≥40 (p-value for trend: < 0.0001). Adjusted 30-day mortality risk for patients undergoing CAS in hospitals with ≥40 past-year CAS was 0.5 (95% CI: 0.4–0.7), relative to patients treated in hospitals performing < 10 CAS. There was a significant downward trend in mean LOS with greater physician and hospital experience. Increasing annualized CAS experience had a consistent inverse association with mortality.

Conclusions: Larger physician and hospital CAS volume is associated with more favorable peri-procedural outcomes in Medicare patients. Real-world studies evaluating CAS performance should consider accounting for experience.

673. Abstract withdrawn by author.

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675. Probabilistic vs. Deterministic Linkage of Large Device Registries to Medicare Data

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Background: Record linkage can enhance data quality in comparative effectiveness research. Deterministic linkage, a method often relying on exact matches on one or more linkage variables, can result in false-negative linkages when values for linkage variables are missing or have errors. Probabilistic linkage could overcome this problem.

Objectives: To assess the performance of probabilistic vs. deterministic linkage of a medical device registry with Medicare claims data.

Methods: We linked hospitalizations for implantable cardioverter-defibrillator (ICD) placement in a CMS ICD registry and Medicare inpatient files. We employed probabilistic linkage using admission date, Social Security number, birth date, sex, and provider ID. We assessed the distribution of linkage weights and the number of linked records at different weights. We also calculated the positive predictive values (PPVs) of the linkages at various weight cutoffs using the duplicate method. We then compared the performance of probabilistic vs. deterministic linkage using PPV = 90 as a cutoff for probabilistic linkage, and identified patterns of nonmatching for those linked by probabilistic but not by deterministic linkage.

Results: Of 16,225 linkable records for ICD placements, 14,667 (90%) to 9,638 (63%) were linked using different cutoffs of the linkage weight ranging from 7 to 26. Corresponding PPVs included 62% at linkage weight 14 and 99.6% at weight 26. Deterministic linkage requiring exact matching for the same variables identified 9956 (61%) matches between the same data sources, 12% less than the number of matches identified by probabilistic linkage using weight 20 (PPV = 90%) as a cutoff. There were 1,402 pairs matched by probabilistic linkage but not by deterministic linkage. Among these, 90% had discrepant values for only 1 variable and 10% had nonmatching values for two or more variables.

Conclusions: Probabilistic linkage can increase the number of linkages moderately by reducing false-negatives compared to deterministic linkage in our ICD registry example. Further studies are needed to understand the validity of the duplicate method to calculate PPVs and identify situations when probabilistic linkage provides greater benefits.

676. Descriptive Epidemiology of Medical Device Use among Patients with Breast, Lung or Prostate Cancer in the National Inpatient Sample

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Background: Cancer patients may undergo treatment with a medical device for conditions in addition to their cancer diagnosis. Little is known about cancer patients undergoing implantable medical device (IMD) procedures.

Objectives: To explore the epidemiology of cancer patients undergoing IMD procedures.

Methods: We conducted an exploratory analysis of Nationwide Inpatient Sample (NIS) data from 2000 to 2009. We used ICD-9 codes to identify patients with inpatient stays for cardiovascular, orthopaedic and urologic procedures. Cancer patients were identified using ICD-9-CM codes for lung (162–163.9), breast (174–174.9), and prostate (185) cancer. Characteristics of cancer patients undergoing IMD procedures were compared with non-cancer patients undergoing the same procedures.

Results: From 2000 to 2009, breast, prostate, and lung cancer patients underwent 5,656, 18,268, and 11,549 cardiovascular, orthopaedic, or urology implant procedures, respectively. Among those with breast cancer, 20% were cardiovascular, 64% orthopaedic, and 15% urologic procedures. Among those with prostate and lung cancer

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respectively, 32% and 27% were cardiovascular, 38% and 38% orthopaedic, and 31% and 36% urologic procedures. Breast, prostate, and lung cancer patients comprised <2% of all cardiovascular, orthopaedic, or urologic procedures in this time period. Length of stay (LOS) was higher among those with cancer undergoing IMD procedures compared to non-cancer. Among lung cancer patients, hospital charges were higher for all procedures compared to non-cancer patients; this increased cost was not observed among breast and prostate cancer patients.

Conclusions: Preliminary results indicate that many cancer patients undergo IMD procedures. These patients experience longer LOS and higher costs for IMD procedures. Our analysis informs research to identify medical device related patterns of care among cancer patients, and lays a foundation for future research aimed at understanding the relationship between IMDs, cancer treatment, and patient outcomes.

677. Estimates of Invasive Home-Use Medical Device Adverse Events Resulting in Hospitalization

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Background: The number of invasive medical devices (implanted/intra-orifice) used outside the hospital continues to increase; the public health burden of serious adverse events (AE) associated with these devices is unknown.

Objectives: To determine national estimates for AEs associated with invasive home-use medical devices resulting in hospitalization.

Methods: From October 2008 to September 2009, reports of 347 medical device–associated AEs for invasive home-use devices resulting in hospitalization were collected using the National Electronic Injury Surveillance System (NEISS), which collects information on product-related injuries from the emergency department records of a national stratified probability sample of hospitals. The reports were used to estimate annual number of medical device–associated adverse events as well as number of AEs associated with specific devices [Global Medical Device Nomenclature (GMDN)], injury diagnoses, and demographics. A phone survey of injured patients was conducted to gather information on event details and patient experience

Results: Total estimated number of AEs associated with invasive home-use devices was 34,042 (95% confidence interval = 9,726–58,358). Device groups with the highest estimates of adverse-events were cardiovascular (defibrillators, cardiac pacemakers), orthopedic (joint prostheses, cervical spine immobilization systems), and gastro-urological (gastrointestinal tubes, peritoneal dialysis catheters). Prevalent types of AEs involved device infection, dislocation, shunt malfunction, and inappropriate pacing. Approximately 70% of patients did not receive training/instructions for device operation.

Conclusions: Serious adverse events associated with invasive home-use devices account for a significant estimated number of product-related emergency department visits. Patient education regarding their device may impact the occurrence and outcome of AEs. Future analyses of AEs will provide better insight into this issue.

678. Coding of Ophthalmic Medical Device Adverse Event Reports: A Comparison of FDA Patient Problem Codes and MedDRA

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Background: Medical Device adverse event reports in the US are submitted to FDA using a coding thesaurus known as FDA Patient Problem Codes. Drug adverse event reports are submitted to FDA using MedDRA codes.

Objectives: This study looks at the similarities and differences between both thesauri as they relate to ophthalmic Medical Device reports.

Methods: In March 2011, MedDRA was added to Alcon's safety database for Medical Devices. Double coding using FDA Patient Problem Codes and MedDRA codes ensued. The goal of double coding was to determine the adequacy of MedDRA coding for medical device safety/risk assessment purposes. At the end of March 2012, a 1-year study of coding for safety will occur. At the time of this abstract, a 100 case sample from January 2012 was extracted from the database along with both sets of codes. Preliminary data comparing one-to-one matches, similar medical concept matches, and non-matches were made.

Results: One hundred medical device adverse event cases containing 164 adverse events were extracted from the medical device safety database. Fifty-two percent (85 codes) had one-to-one matches. Eighteen per cent (29 codes) were similar in medical concept, but were not exact matches. In 30% (50 codes), there was no concordance between FDA Patient Problem Codes and MedDRA.

Conclusions: Preliminary analysis of coding ophthalmic medical device reports with MedDRA suggests that MedDRA may be useful for individual and aggregate safety analysis of ophthalmic medical device reports. Where MedDRA terms did not match Patient Problem Codes, MedDRA terminology was more specific in identifying an event. These results are tempered by the fact that a limited dataset was used for analysis. A more thorough analysis using 12 months worth of coding will be available after April 1, 2012.

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679. Cost-Utility Analysis of Antihypertensive Medications in Nigeria: A Decision Analysis

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Background: Prevalence of hypertension is on the rise in most African countries while control remains poor. Many effective drugs are available for control of high blood pressure in hypertensive patients living in low income regions. The use of cost-effective drugs will ensure efficient use of financial resources in a low income nation like Nigeria.

Objectives: The objective of this study was to evaluate the cost-effectiveness of drugs from four classes of antihypertensive medications for use in management of hypertension in Nigerians without compelling indication to use a particular antihypertensive drug.

Methods: The study employed decision analytic modeling. Interventions were obtained from a meta-analysis. The Markov process model calculated clinical outcomes and costs during a life cycle of 30 years of 1,000 hypertensive patients stratified by three cardiovascular risk groups, under the alternative intervention scenarios. Quality adjusted life year (QALY) was used to quantify clinical outcome. The average cost of treatment for the 1,000 patient was tracked over the Markov cycle model of the alternative interventions and results were presented in 2010 US Dollars. Probabilistic cost-effectiveness analysis was performed using Monte Carlo simulation, and results presented as cost-effectiveness acceptability frontiers. Expected value of perfect information (EVPI) and expected value of parameter perfect information (EVPPI) analyses were also conducted for the hypothetical population.

Results: Thiazide diuretic was the most cost-effective option across the three cardiovascular risk groups. Calcium channel blocker was the second best for moderate risk and high risk with a willingness to pay of at least 2000$/QALY. The result was robust since it was insensitive to the parameters alteration.

Conclusions: The result of this study showed that thiazide diuretic followed by calcium channel blocker could be a feasible strategy in order to ensure that patients with hypertension are better controlled.

680. Pharmacoeconomic Analysis of the Basic Care of Hypertension and Other Associated Cardiovascular Risk Factors

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Background: The intensive efforts in the management of cardiovascular risk factors pull a higher cost of the treatment.

Objectives: The objective of this study is to estimate the impact of hypertension on the cardiovascular complications and to analyze its cost of care.

Methods: This is a prospective study between November 2010 and February 2012, concerning 742 patients with essential hypertension followed in the outpatient of cardiology, at the city of Rabat.

Results: According to the classification of Framingham, 437 (58.9%) have complicated hypertension (i.e., associated with diabetes and/or nephropathy). Diabetes was the main cardiovascular disease associated with hypertension, it was found in 205 (47%) patients. The annual direct cost of the care per hypertensive patient without any complications has been estimated in an average of 698.2 Euro vs. 837.7 Euro for the hypertension associated with other cardiovascular risk factors. Laboratory tests represented a small proportion of this cost, between 6.6% (46.3 Euro) for patient with hypertension disease without any health problem and 8.64% (72.3 Euro) for hypertension associated with other cardiovascular risk factors. While the therapeutic treatment of hypertension represents the largest proportion of the global cost 578.3 Euro for hypertensive patient without any health difficulties 596.6 Euro for hypertension associated with other cardiovascular risk factors. The therapeutic annual management for hypertensive patients without any complications estimated to 138.6 Euro [-7.1–284.3] and 266 Euro [37.4–494.6] for monotherapy and double-therapy respectively. While the therapeutic annual management for hypertensive patients associated with other cardiovascular risk factors was estimated to 138.6 Euro [-7.1–284.3], 319 Euro [181.5–456.4], 473.1Euro [325.1–621.1] and 723.5 Euro [571.8–875.3], for monotherapy, double-therapy, triple-therapy and quadritherapy respectively.

Conclusions: In Morocco, the treatment remains expensive because of the low purchasing power and lack of widespread coverage by health insurance.

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681. The Cost of Hospitalization of Hip Osteoarthritis Patients in France in 2010

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Background: The last study evaluating the cost of osteoarthritis in France dated on 2005.

Objectives: Evaluate the cost of hospitalization of hip osteoarthritis patients in France in 2010.

Methods: For hospital stays (medical, surgery and obstetrics) and f or patients treated under Follow-up care and Rehabilitation (formerly "halfway house"), use of the PMSI data .The evaluation we carried out is based on the last 2 years of available data – 2009 and 2010.

Results: In France, around 90,000 patients are treated every year in hospitals for hip osteoarthritis (figures from 2009/2010). Fifty-five percent of these patients are female, and 45% are male, with an average age of 70. The average hospital stay was 9 days (9.5 average per patient per year). The average annual treatment cost for one patient is estimated at around €7100 44% of patients are then treated with rehabilitation, of which 66% are women. The average age of these patients is 73. Each patient stays for an average of 32 days, either full or partial hospitalization with functional reeducation or medical follow-up treatment. The average annual treatment cost of a patient in rehabilitation is estimated at around €6,593. In total, the annual cost of a patient treated in hospital (hospital + rehabilitation) for hip osteoarthritis in 2010 is estimated at €10,000. In total, the overall annual cost for all patients undergoing hospital treatment in 2010 is estimated at €1 145 million euros.

Conclusions: The last study evaluating the cost of osteoarthritis in France (COART – Le Pen and coll, Revue du rhumatisme, December 2005) reported 127 000 short-stay admissions, 175,000 follow-up and/or rehabilitation treatment days, and 118,000 knee or hip replacements, the overall cost of hospitalizations is therefore 820 million euros in 2002. Our evaluation demonstrates that this cost evaluation is outdated, as the amount is lower than the overall cost of hospitalizations linked to osteoarthritis of the hip.

682. The Medication Adherence Report Scale (MARS-5) in a Swedish Sample with Bipolar Disorder – A Pilot Study

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Background: Bipolar disorder (BD), a chronic mood disorder, is often treated with mood stabilising medications. For patients with BD, non-adherence (20–50%) is associated with cognitive impairment, increased number and lengths of relapses, and hospitalisations. Medication Adherence Report Scale-5 (MARS-5) and the four-item scale Morisky Medication Adherence Scale (MMAS-4) measures adherence to medical treatments. They have not been compared in a sample with BD.

Objectives: To test the functionality of the Swedish translation of the MARS-5 and to compare this questionnaire with the MMAS-4 in a sample using mood stabilising medicines for BD.

Methods: The sample (n = 47, 70% women), in this cross-sectional pilot study, was recruited through patient education sessions and meetings, newsletters and home pages of Patient Association in Sweden. The participants received a questionnaire including the Swedish translations of the MARS-5 and the MMAS-4, and background questions. Reliability was examined for internal consistency (Cronbach's α) and test-retest (intraclass correlation [ICC], MARS-5: Pearson's correlation coefficient [r], MMAS-4: Spearman's rho [ρ]). The acceptability of the MARS-5 was examined with a correlation analysis (MARS-5 vs. MMAS-4) and for face validity.

Results: Adherent behaviour was categorised with 53.3% of the sample when using the MARS-5 and 82.6% with the MMAS-4. The internal consistency was 0.66 for the MARS-5 and 0.37 for the MMAS-4. The test-retest of the MARS-5 resulted in r = 0.90 and ICC = 0.91. For the MMAS-4 the corresponding values were ρ = 0.84 and ICC = 0.85. The correlation between the MARS-5 and the MMAS-4 was 0.55. The face validity resulted in four comments regarding difficulties in answering the MARS-5.

Conclusions: The Swedish translation of the MARS-5 showed good psychometric properties. This adherence questionnaire ought to be used when measuring self-reported adherence in a Swedish sample with BD.

683. The Impact of Abuse Deterrent Formulations on Outcomes Associated with Prescription Opioid Abuse

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Background: Prescription opioid abuse (RxOA) is behavior associated with serious outcomes, overdose, addiction, and death. The FDA has approved both immediate-release (IR) and extended-release (ER) opioids designed to deter common forms of tampering, defined as manipulating a dosage form to change its drug delivery, and includes crushing/chewing then swallowing; crushing ? snorting; and crushing, dissolving, ? injecting. These formulations are often referred to as abuse deterrent formulations (ADF), although no opioid yet has that designation in its

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prescribing information; substantial evidence of abuse deterrence in the community is needed. However, if ADF formulations are successful in deterring abuse, it is reasonable to expect to change health-related outcomes.

Objectives: To evaluate the potential impact of RxOA-associated outcomes after the introduction of an ADF designed to deter abuse by tampering.

Methods: An opioid Budget Impact Model [AG White, et al. *Appl Health Econ Health Policy* 2009;7(1):61–70] was utilized to evaluate the impact on RxOA-associated outcomes after an ADF is introduced in the market. The model accounts for an ADF's population exposure, its effectiveness to deter abuse, and methods of abuse. The metric used was the number of episodes/medical events avoided for emergency department [ED] visits, hospitalizations, and injection-related diseases. Population exposure was modeled equally for each of the ER and IR opioids and was varied from 25 to 75%. Effectiveness was modeled using a range from 25% to 75%.

Results: The model estimates an ADF that is 25% effective in deterring abuse-by-tampering could avoid 42,809–128,426 ED visits, 28,350–85,050 hospitalizations, and 5,959–17,833 injection-related diseases based on 25% or 75% population exposure, respectively. Alternately, an ADF that is 75% effective could avoid 128,426–385,157 ED visits, 85,050–255,071 hospitalizations, and 17,833–53,543 injection-related diseases based on 25% or 75% exposure, respectively.

Conclusions: An ADF has the potential to markedly reduce RxOA related outcomes in the US, and is dependent on both the product's effectiveness and having sufficient population exposure.

684. Factors Associated with Quality of Life in Patients with Chronic Hepatitis B in Brazil

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Background: Studies of quality of life related to health are important for evaluation of chronic diseases, but are scarce for chronic hepatitis B (CHB).

Objectives: Evaluate the quality of life, socio-economic and demographic aspects, factors related to health, disease diagnosis and type of health services utilized by patients with CHB, from April to July 2009, using medicines provided by National Health System (SUS).

Methods: A questionnaire was developed to collect data. To assess the quality of life was used EuroQol-5D (EQ-5D) questionnaire.

Results: Were interviewed 102 patients, mean age of 48.17 years, predominantly male, married and depends exclusively on SUS, 67.0% of patients started treatment with lamivudine. Low mean of quality of life were observed for patients with low education, who were hospitalized, with poorer perception of health status, which failed to perform daily activities, in bed due to illness, had no health insurance, with later stages of the disease and had no income in the last month ($p < 0.05$). For the multiple regression model, the variables in the final model were: sex, perceived health status, failure to perform daily activities and in bed due to illness, classification of health status, income in the last month being responsible for 27.53% of the variability of the quality of life measure. Reductions of quality of life were observed in the mean value for females (-0.0819), for those who had no income in the last month (-0.0747) compared to who had; who perceived their health worse (-0.1579), compared with better perception and those with cirrhosis (-0.0364), hepatocellular carcinoma (-0.3449) and transplantation (-0.1990) compared to patients without cirrhosis. Analysis of residues showed that the model shows good fit, with an average close to zero, no violation of the assumption of homoscedasticity and the absence of outliers.

Conclusions: CHB presented an important impact on quality of life of patients and these results may be useful for pharmoeconomic evaluations.

685. The Impact of Therapy Intensification to Blood Pressure Outcome on the Ambulatory Hypertensive Patients: An Observational Study in Indonesian Hospital

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Background: Intensive blood pressure (BP) management reduced the cardiovascular event. Therapy intensification (TI) improved BP level better than medication adherence; however, TI in clinical setting was relatively low and became the barrier in BP control.

Objectives: To compare TI-score and BP level between Group 1 (n = 401) patients with CVD risk factors and BP target of ≤130/80 mmHg; Group 2 (n = 268) no risk and BP target of ≤140/90 mmHg. To know if the effect of TI was better than adherence on BP level.

Methods: The cohort study was done in four hospitals January to May 2011. The subject criteria were adult, hypertension, ≥2 ambulatory visits; and not in hemodialysis procedure. TI and adherence were calculated using

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standard-based method and mean possession ratio respectively. Subject blood pressure (BP) was categorized into four subgroups, i.e., good; bad; improved; and declined BP control. Comparison was applied to TI-score, adherence, and target–final visit BP level (ΔSBP/ΔDBP). The relationship between TI-score and BP control were analyzed with Pearson correlation.

Results: The most frequently prescribed hypertensive drugs were similar between groups, i.e., amlodipin, valsartan, and bisoprolol. Group 1 had older age; more visit frequencies, more males, and less hypertensive drugs ($p < 0.05$). Final BP in both groups was higher than the target; The ΔSBP/ΔDBP in Group 1 and 2 was (-) 13.9 ± 17.4/(-) 1.0 ± 9.4 mmHg and (-) 9.0 ± 18.5/ 0.9 ± 9.3 mmHg ($p < 0.05$). Adherence level was high (0.8); patients with final BP met the target was low (40%); and TI score was low (-0.4) ($p > 0.05$). BP control subgroups consisted bad 45.9% vs. 38.1%, good 13.2% vs. 23.5%, improved 23.9% vs.17.5%. TI-score and SBP had significant correlation with medium level ($r = 0.4$–0.6), TI correlated weakly with DBP ($r = 0.2$–0.4), but there was no correlation between adherence and BP level.

Conclusions: Group 1 and 2 had similar TI-score, adherence level, and proportion of patients met the target. Group 1 had worse outcome based on the proportion of good and bad control subgroups; and ΔSBP/ΔDBP level. TI-score correlated with SBP significantly in medium level.

686. Osteoarthritis in France the Cost of Ambulatory Care in 2010

Charles Taieb. *Public Health and Quality of Life, PFSA, Boulogne Billancourt, France*.

Background: In France, the cost of an osteoarthritic patient has not been estimated for several years. (2005)

Objectives: The aim of the study was to evaluate the annual cost of the treatment given to osteoarthritic patients by GP.

Methods: The cohort was made up of patients who were diagnosed with osteoarthritis between April 2009 and March 2010 (IMS Disease Analyzer database) The cost includes all medical cost to the patients in the cohort, and colligated in the Disease Analyzer database (all consultations with GPs and all resulting drug prescriptions). The evaluated cost is therefore the annual cost of treatment given to an osteoarthritic patient.

Results: Eighteen thousand and nine hundred seventy-six patients suffering from osteoarthritis were followed. For these patients, who had an average age of 66, all consultations with GPs as well as all resulting drug prescriptions were valued both in terms of societal cost and cost to health insurance. The average annual cost of disease management by a GP of a patient suffering from osteoarthritis is therefore valued at €755 societal cost, of which around 60% (€447) is paid by health insurance. The annual cost of treatment by a GP of a patient suffering from hip osteoarthritis is significantly lower at the societal level (€715) than at the health insurance level (€425) compared to patients suffering from osteoarthritis in the knee or elsewhere, despite their higher age.

Conclusions: No literary data evaluating the cost of an osteoarthritic patient currently exists. The closest data is that produced by a COART® France study (Le Pen and coll, Revue du rhumatisme, December 2005). The prevalence of osteoarthritis has been estimated at around 4 million sufferers, even though this figure may be conservative, we can estimate that the cost of osteoarthritis treatment is around 3 billion euros. We are sure that further data will be added to existing ones.

687. Abstract withdrawn by author.

688. Lund Integrated Medicines Management (LIMM)-Model Improves the Health Care Process and Patient Outcomes

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Background: The effects from clinical trials are hard to achieve in standard care and there is risk of negative patient consequences and costs, especially in elderly admitted to hospital.

Objectives: To develop a systematic model for improving therapeutic outcomes for the patient and the society.

Methods: Analysis of problems in the standard patient medication process starting at admission. A structured model based on medication- reconciliation and review including specific tools, checklists and responsibilities was developed. The clinical pharmacist is the catalyst for improvement in the care team, but each member has their specific responsibilities. Studies were performed at medicine wards on a university and local hospital. All studies were prospective, controlled and compared LIMM-activities to "standard care. Blinded evaluations and established criteria and statistical tests were used.

Results: Fourteen scientific publications, 4 PhD- and 30 MSc-thesis has been performed. Among 210 patients there was a greater decrease in the number of inappropriate drugs in the intervention group (60% [95% CI 51–67%] vs. 44% [95% CI 34–52%]; [$p = 0.011$]).There was six revisits to hospital in the intervention group judged as "possibly, probably or certainly drug related", vs. 12 in the control group ($p = 0.047$). Primary care contact due to medication errors was reduced. In the intervention group 11/248 (4.4%) needed care because of medication errors compared with 16/179 (8.9%) in the control group ($p = 0.049$). There was a reduced risk of any consequences due to medication errors, $p = 0.005$. LIMM-

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model is also time and cost saving. The pharmacist spend 1 hour for each patient and physicians and nurses at hospital and in primary care saves at least 2 hours. Cost savings of €370, for each intervention cost of €42 and gained utility of 0.005 was calculated using a probabilistic decision tree model. The intervention was cost saving at a 98% chance in spite of the underlying uncertainties in parameter values.

Conclusions: The LIMM-model has successfully been researched introduced in Skåne and is spreading nationally based on demand for patient safety and improved pharmacotherapy in the elderly.

689. Topiramate Use in Pregnancy and Risk of Oral Clefts

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Background: Topiramate (TPM) is an antiepileptic drug also used for migraine prophylaxis. Combined with phentermine, TPM is being evaluated as treatment to promote weight loss. Some observational studies have suggested an elevated risk of oral clefts in infants whose mothers used TPM in early pregnancy.

Objectives: To evaluate the association between TPM use in early pregnancy and risk of oral cleft (OC) in offspring.

Methods: We conducted the first phase of a retrospective cohort study using 1997–2011 automated data from four sources: HealthCore and OptumInsight (commercial insurance claims from throughout the US), Thomson Reuters (Medicaid claims from several states), and Northern California Kaiser Permanente (electronic health records). We compared the prevalence of OCs in infants of women exposed to TPM in the first trimester of pregnancy (TPM cohort) with the prevalence in two comparator cohorts: infants of women formerly exposed to TPM or other antiepileptic drugs (FE cohort) and infants of women with similar medical profiles to the TPM cohort (SMP cohort). To control for confounding, we used stratification and standardization to the TPM cohort for individual variables and propensity score decile.

Results: Overall, the birth prevalence of OCs was 0.36% (7/1945) in the TPM cohort, 0.16% (21/13,512) in the FE cohort, and 0.07% (9/13,614) in the SMP cohort. Standardized by site, the prevalence ratio (PR) for TPM vs. FE was 2.36 (95% CI: 0.99–5.59) and for TPM vs. SMP, 5.44 (95% CI: 2.03–14.61). Adjustment for other covariates one at a time yielded very similar results. Standardized by propensity score decile and site, for TPM vs. FE the PR was 2.45 (95% CI: 0.97–6.18) and for TPM vs. SMP, 6.46 (95% CI: 2.07–20.17). OC prevalence did not increase with TPM dose.

Conclusions: The preliminary results determined only from automated data in this multi-database study show first trimester topiramate exposure was associated with an elevated risk of OCs. The final analysis will rely on outcomes validated through review of medical records or longitudinal claims histories.

690. Discontinuation of Antiepileptic Drugs in Pregnancy; a UK Population Based Study in The Health Improvement Network (THIN)

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Background: A number of women of childbearing age take antiepileptic drugs (AEDs) for the treatment of epilepsy or bipolar disorders. Many of these women face a dilemma on whether to continue their medication in pregnancy because of the teratogenic effect of AEDs.

Objectives: To determine whether pregnancy is a major determinant for discontinuation of AEDs.

Methods: A cohort study of pregnant women receiving AEDs in UK primary care was conducted. A total of 174,055 pregnancies in women aged 13–55 years were identified in THIN. In 934 women, AEDs were prescribed in the three months before pregnancy and time to last consecutive AED prescription in pregnancy was estimated whereby discontinuation of therapy was defined by a gap of more than three months between prescriptions. Twice as many non-pregnant women receiving AEDs were randomly selected within five year age bands to match the age distribution of pregnant women, and matched on indication for AEDs with pregnant women. Cox's regression was used to compare the likelihood of discontinuing AEDs between pregnant and non-pregnant women.

Results: Pregnant women with epilepsy were twice as likely to cease AEDs compared to non-pregnant women (Hazard Ratio [HR]:2.00, 95% confidence interval [CI]:1.62–2.47). Of 745 pregnant women with epilepsy, 601 (80.7%) continued treatment into pregnancy and 465 (62.4%) to the end of the second trimester. Of 1490 non-pregnant women with epilepsy, 1242 (83.4%) and 1071 (71.9%) continued for comparable time periods. Pregnant women with bipolar disorder were three times as likely to cease AEDs compared to non-pregnant women (HR:3.07, 95% CI:2.04–4.62). Of 54 pregnant women with bipolar

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disorder, 27 (50.0%) continued into pregnancy, and only 8 (14.8%) to the end of the second trimester. In 108 non-pregnant women with bipolar disorder, 82 (75.9%) and 58 (53.7%) continued for comparable periods.

Conclusions: Pregnancy is a determinant for the discontinuation of AEDs during pregnancy, especially in women with bipolar disorder or depression despite the severe consequences associated with untreated mental health problems.

691. Lamotrigine Use in Pregnancy and Risk of Orofacial Cleft Risk, an Update

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Background: A signal was found for maternal first trimester lamotrigine (LTG) exposure and the risk for isolated orofacial clefts (OCs), especially for isolated cleft palate (Holmes, 2006). The signal was examined in the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database (Dolk, 2008). No significantly increased risk of OCs was found, either for isolated orofacial clefts or for isolated cleft palate relative to other non-chromosomal registrations. However, the confidence intervals were wide due to the small number of LTG monotherapy.

Objectives: To investigate whether first trimester exposure to LTG monotherapy is specifically associated with an increased risk of OCs relative to other malformations.

Methods: Population-based Case–Control study with malformed controls was performed using updated EUROCAT antiepileptic-study database. The dataset included 151,043 live births, stillbirths, or terminations with malformations among 6.2 million births in 20 European countries from 1995 through 2009. Cases were 8,570 nonsyndromic OC registrations, of whom 7,279 were isolated, 3,022 were cleft palate (CP) and 2,442 were isolated CP. Controls were 122,728 nonchromosomal, non-OC registrations. We compared first trimester LTG and antiepileptic drug (AED) use vs. nonepileptic non-AED use adjusting for maternal age.

Results: There were 130 LTG exposed (78 mono- and 52 polytherapy) registrations. The adjusted odds ratios (ORs) for LTG monotherapy vs. no AED use were 1.07 (95% CI 0.43–2.46) for OC relative to other malformations, 0.91 (95% CI 0.37–2.24) for isolated OC, 1.04 (95% CI 0.26–4.25) for CP, and 1.29 (95% CI 0.32–5.26) for isolated CP. The adjusted ORs for any AED use vs. no AED use were 1.34 (95% CI 1.04–1.72) for OC, 1.16 (95% CI 0.86–1.55) for isolated OC; 2.17 (95% CI 1.56–3.03) for CP, and 1.81 (95% CI 1.21–2.70) for isolated CP.

Conclusions: This update does not change the conclusion of the original study: we found no evidence of an increased risk of isolated orofacial cleft relative to other malformations for lamotrigine monotherapy exposure in the first trimester, nor any evidence of an increased risk for isolated cleft palate.

692. Methods for Linking Mothers and Infants within Health Plans for Studies of Medication Safety in Pregnancy

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Background: Research on medication safety in pregnancy often utilizes health plan and birth certificate data. This requires accurate mother-infant linkages.

Objectives: To describe approaches used in a multi-site research program to link mothers and infants with each other and with birth certificates, and to explore how linking methods affect the composition of the final population.

Methods: We developed guidelines for mother-infant linkage using health plan data including birth registries, insurance subscriber numbers, and names and addresses at 11 plans participating in the Medication Exposure in Pregnancy Risk Evaluation Program. Each site adapted the guidelines to its data resources. Two sites linked health plan with birth certificate data to identify additional mother-infant pairs not found through health plan data

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alone. Methods for linking to birth certificates varied by state. For deliveries in 2001–2007, we calculated the proportion of deliveries that could be matched to an infant. We also compared the populations identified using different linking methods and data sources.

Results: Two sites had preexisting birth registries linking more than 99% of deliveries to infants. A third site using Medicaid data linked 93% of 340,135 infants to mothers and 95% to birth certificates (91% to both) with a probabilistic algorithm. For the remaining eight sites, 86% of 299,260 deliveries could be linked to infants using a deterministic algorithm (range, 74–99%), and 92% of resulting pairs could be linked to birth certificates. At two sites, using birth certificate data to augment mother-infant linkage increased the representation of mothers who were Hispanic or non-white, younger, less educated, and insured through Medicaid.

Conclusions: Data resources for mother-infant linkage vary widely across health plans, requiring tailored approaches. Across diverse plans, a high proportion of mothers (74–99%) can be linked to infants using detailed, comprehensive algorithms. Using birth certificate data to augment mother-infant linkage can increase representativeness of the population available for research.

693. Utilization of Antiepileptic Drugs in Florida Medicaid Women with Epilepsy of Childbearing Age

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Background: Previous studies have demonstrated an increased risk of having a child with a birth defect in women with epilepsy (WWE) taking antiepileptic drugs (AEDs). Concerns of multiple malformations risks for valproate arose in 2004, and were addressed by a FDA safety warning in 2009. Current treatment guidelines for women with pregnancy or pregnancy intent recommend monotherapy, avoiding valproate, and using folic acid.

Objectives: This study aims to investigate secular trends in utilization of AEDs in Florida Medicaid WWE of childbearing age, to estimate the extent of polytherapy, and to compare the use of first and second generation AEDs.

Methods: Study participants consisted of female Florida Medicaid beneficiaries diagnosed with epilepsy, continuously enrolled over 6 months, and aged 12–45 from 2004 to 2009, resulting in 2847–3749 subjects across study years. Eighteen AEDs were categorized into first and second generation. Continuous use was defined as at least 2 consecutive prescriptions totaling more than 30 days of supply. Polytherapy was defined as 2 or more AEDs continuously used for at least 60 overlapping days. Annual prevalence was estimated and compared among AEDs.

Results: Across study years, between 40.3% and 46.0% of WWE in childbearing age used polytherapy. From 2004 to 2007, AEDs most used in monotherapy were: carbamazepine (18.3–14.9%), valproate (18.2–14.1%), and phenytoin (16.6–12.9%). Levetiracetam replaced phenytoin in the top three drugs and became the most commonly used monotherapy in 2008 (14.3%). As for polytherapy, phenobarbital/phenytoin (3.2%), carbamazepine/valproate (3.1%), and phenytoin/valproate (2.9%) were the top three most commonly used combinations in 2004, whereas, lamortrigine/levetiracetam (2.7–2.9%), levetiracetam/topiramate (2.7–2.8%), and lamortrigine/topiramate (2.1–2.6%) were the top three combinations in 2008 and 2009.

Conclusions: Second generation AEDs are replacing the first generation in either add-on therapy or monotherapy after 2008, though the prescribing rate of valproate in monotherapy remains high, and polytherapy use has not declined. This emphasizes the need for more comprehensive information on teratogenic risk.

694. Prenatal Diagnosis of Birth Defects and Potential Selection Bias in Studies of Birth Defects Measured after Birth: How Severe Is the Problem?

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Background: Termination of pregnancy at prenatal diagnosis is a potential source of selection bias in epidemiologic studies of birth defects if such studies measure only defects diagnosed at or after birth.

Objectives: To estimate the extent of selection bias due to pregnancy termination after prenatal diagnosis in a cohort of pregnancies reconstructed from observable pregnancy outcomes.

Methods: We reconstructed the cohort of pregnancies ending in calendar year 2007 using data on spontaneous and induced abortions from the Danish National Registry of Patients (DNRP), and data on live and stillbirths after gestational week 28, from the Danish Medical Birth Registry. Since 2005, the DNRP has registered pregnancies with birth defects detected and terminated following prenatal diagnosis after gestational week 12. We calculated proportion of pregnancies with birth defects terminated at prenatal diagnosis among all observable pregnancies with birth defects.

Results: We reconstructed 89,639 pregnancies ending in 2007, 28.4% of which ended in a spontaneous or induced abortion recorded in the DNRP. Overall, 2,957 pregnancies had a record of a birth defect either terminated prenatally or recorded after birth. The most prevalent birth

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defects were malformations of musculoskeletal (984, 33%); circulatory (553, 19%); and digestive (262, 9%) systems. Overall, 253/2,957 (proportion 0.08; 95% CI: 0.07–0.10) pregnancies were terminated after prenatal diagnosis. Birth defects with highest proportions of prenatal terminations were chromosomal abnormalities (109/162; proportion 0.67; 95% CI, 0.59–0.74); and nervous system defects: 55/134 (proportion, 0.41; 95% CI, 0.33–0.50). For most of other types of birth defects proportion of prenatal terminations did not exceed 0.05.

Conclusions: Severity of selection bias due to prenatal diagnosis and termination varies by type of defect. Chromosomal abnormalities and defects of nervous system will be substantially underascertained by relying on postnatal measurement. For other types of birth defects, the bias due to prenatal diagnosis and termination is weaker.

695. Incidence and Time-to-Onset of Hematologic Events among Genotype 1 Chronic Hepatitis C Patients Being Treated with Pegylated Interferon and Ribavirin

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Background: We studied the incidence and time to onset for anemia, leukopenia, and thrombocytopenia among patients in a large integrated health care plan during treatment with pegylated interferon and ribavirin (Peg-IFN/RBV) for hepatitis C virus (HCV) genotype 1 infection.

Methods: Northern California Kaiser Permanente databases were used to identify patients and retrieve all information. We included adults with at least 5 weeks of Peg-IFN/RBV therapy during 2005–2009, and ≥11 months continuous enrollment prior. We excluded patients with hepatitis B or HIV co-infection, HCV clinical trial participation, or in pre-transplant care. Outcomes were defined as first evidence of anemia (hemoglobin ≤10 g/dL), leukopenia ($<1{,}500$ WBC/μL) and thrombocytopenia ($<50{,}000$ platelets/μL) assessed by week (1–52) of treatment.

Results: Of 850 eligible patients, 63% were men, mean age was 52 years, and 57% were White non-Hispanic. Most (78%) had treatment for at least 24 weeks (mean: 38 weeks). Pre-existing conditions included diabetes (13%) and cirrhosis (12%). The cumulative incidence of anemia during treatment was 35%, leukopenia 8% and thrombocytopenia 9%. Onset occurred within the first 12 weeks of treatment for 54% of patients with anemia, 44% with leukopenia, and 67% with thrombocytopenia, and within the first 24 weeks for 79%, 65%, and 82%, respectively. Ribavirin dose reductions were evident for 20% of patients and 35% of patients received erythropoietin during treatment. Among the 92 cirrhotic patients without a recent history of the outcomes, the timing of onset was similar and the cumulative incidence was 36% for anemia, 15% for leukopenia, and 25% for thrombocytopenia.

Conclusions: In this cohort of genotype 1 chronic hepatitis C patients, with or without cirrhosis, receiving dual therapy with Peg-IFN/RBV, we found hematologic outcomes were most frequent during the first 12 weeks of treatment. This background pattern and prevalence of severe hematologic outcomes should be considered when additional HCV antivirals are being administered concomitantly.

696. ARITMO Project. Torsade de Pointes Associated to Antimicrobials, Antipsychotics and Antihistamines: An Analysis of the French Spontaneous Reporting Databasexb

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Background: The ARITMO project aims to analyse the Torsade de pointes (TdP) and QT prolongation (QTP) potential of antipsychotics, antimicrobials and H1-antihistamines. As part of this project, French pharmacovigilance data were analysed.

Objectives: To identify signals associating TdP to the ARITMO drugs of interest.

Methods: Reports collected in the French Pharmacovigilance database between January 2000 and August 2010 were analysed. Adverse reactions were coded according to MedDRA, drugs according to ATC. Cases of TdP were identified thrugh: (1) MedDRA preferred term code; and (2) a review of the French pharmacovigilance database free text. Using the case-non case analysis, statistical signals for TdP were searched for all drugs belonging to the following classes: antipsychotics (N05A), antibacterials (J01, J04), antimycotics (J02), antiprotozoals (P01), antivirals (J05) and antihistamines (R06). A potential signal was defined as an association between the event and one of the studied drugs with ≥three cases and a Reporting Odds Ratio (ROR) with 95% Confidence Interval Lower Limit exceeding one. Signals were defined as potential signals associating TdP with one ARITMO drug not mentioned in the restricted Arizona CERT list, which include the drugs increasing the risk of TdP or QTP.

Results: In the subset of the French Pharmacovigilance database used, 213 TdP cases were found (six fatal), 63 (30.6%) of which were related to ARITMO drugs (three

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fatal). Among these, antibacterials (31 cases), antipsychotics (18), and antifungals (13) were the most represented drug. The case non-case analysis identified nine potential signals, six of which concerned ARITMO drugs not included in the Arizona CERT lists. Among them four signals belong to antipsychotics: cyamemazine (four cases), loxapine (three cases), olanzapine (three cases), and tiapride (four cases). The remaining two signals concerned cetirizine (three cases), and fluconazole (four cases, one fatal).

Conclusions: This study found signals of TdP for six drugs. These signals will be further evaluated taking into account concomitant drugs that could explain the occurrence of TdP.

697. An Open Database for Surveillance of QT Prolongation of Marketed Drugs: ECG-ViEW

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Background: QT interval obtained from electrocardiogram (ECG) is essential for surveillance of proarrhythmic potential of drugs. However QT intervals obtained in daily practice cannot be easily used for pharmacovigilance without labor-intensive efforts, because most ECGs are recorded as printed documents or encrypted in a closed commercial ECG management system.

Objectives: To construct an open QT database for surveillance of QT prolongation of marketed drugs by capturing ECG parameters from various ECG data sources in a university hospital.

Methods: ECG data was collected from three data sources in the hospital; scanned ECG printouts, a ECG management system and Electronic Health Record (EHR) system. Optical character recognition (OCR) and web-parsing technique were used for the first two data sources to capture ECG parameters, respectively. The ECG data in EHR were simply copied. To verify the captured ECG parameter obtained by OCR, QTc was calculated with the captured QT and ventricular rate, and then the calculated QTc was compared to the captured QTc. All prescription and laboratory-test results were transferred from the EHR into the QT database. For proof of concept, proportional reporting ratio (PRR) for QT prolongation and amiodarone, a drug known to be associated with QT prolongation, was evaluated with the data from the QT database.

Results: The QT database named ECG Vigilance with Electronic data Warehouse (ECG-VIEW) was constructed. Total of 747,611 of ECG records were captured from 404,348 de-identified individual patients. The accuracy of the OCR technique was 98.4%. Inaccurately captured ECG were manually reviewed and corrected. Of 50.7 million of prescriptions for 1,228 classes of drugs and 65.6 million of laboratory-test results were collected. PRR for the amiodarone and QT prolongation was 5.65 (95% CI, 5.25–6.08)., which was consistent with previous reports.

Conclusions: By using OCR and web-parsing techniques, large amount of ECG records in daily practice can be successfully transferred into ECG-ViEW. It could be used for surveillance of proarrhythmic potential of marketed drugs. The database will be available for public investigators.

698. Are Developing Countries Prepared To Monitor Long-Term toxicities of Antiretrovirals? Findings on Active Surveillance Activities in Sub-Saharan Africa

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Background: Active safety surveillance of medical products (ASSMP) – systematic and proactive approach to detect and evaluate medicine-related risks, is important in identifying and quantifying long-term toxicities of antiretrovirals (ARVs). Recently, active surveillance has provided critical evidence of the safety of first-line ARVs, including stavudine and ziduvodine, and informed revisions of ARV treatment guidelines.

Objectives: We mapped ASSMP capacity in 46 countries in sub-Saharan Africa to identify limitations and propose a systems-strengthening strategy approach.

Methods: Using data collected from a study funded through an interagency agreement between the FDA and USAID, we documented all ongoing and completed ASSMP from 46 countries over the past 5 years. We also studied collaboration among local institutions on medicine safety research. Our definition of ASSMP includes cohort studies, case control studies, registries, prescription event monitoring, drug utilization studies, and phase 4 clinical trials, because all of these study types evaluate the safety and effectiveness of medicines.

Results: ASSMP is implemented in 22 of 46 countries (48%) by academic institutions, public health programs, hospitals, and various international organizations. We found no regional research network conducting ASSMP studies in sub-Saharan Africa. However, ASSMP studies were being conducted in collaboration with institutions in Europe and the United States, where regional networks are more common. ARV-related studies accounted for 15% of all ASSMP, while 41% were malaria related. Medicine use studies, which provide utilization and consumption data to estimate the frequency of adverse events, have been conducted in 13 countries (28%) during the last 5 years.

Conclusions: Active approaches to identify and evaluate medicine-related risks are limited in sub-Saharan Africa. A Systems-strengthening strategy will enhance HIV/AIDS programs to develop collaborative relationships between regulatory authorities, researchers, and academic institutions, and form regional networks to study long-term safety of ARV medicines.

699. Value of Information in Prospective Drug Safety Monitoring Using Claims Databases

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Background: Key to conducting active drug safety surveillance using longitudinal healthcare data is determining if and when there is sufficient evidence to raise a safety alert. We propose to quantify the expected value of the information to be gained through continued monitoring in terms of its potential to reduce health losses among future patients and weigh this against the cost of exposing current patients during continued monitoring.

Objectives: To apply this approach to monitoring the comparative safety of prasugrel (PSG) vs. clopidogrel (CPG) on gastrointestinal (GI) bleeding in a prospective database monitoring system using propensity-score matched sequential cohorts.

Methods: We identified a series of inputs required to calculate expected health losses. Expected rates of death, non-fatal myocardial infarction (MI), and non-fatal stroke on CPG were 1.27, 5.93, and 1.14 per 100 person-years, based on historical data. Relative rates on PSG were 0.95, 0.76, and 1.02 based on TIMI-38 trial data. We assigned gamma prior distributions to the rates of bleeding on CPG and PSG to capture baseline uncertainty; in sensitivity analyses distributions were assigned to PSG's efficacy parameters. MI, stroke, and GI bleed were weighted as 9%, 25%, and 0.1% as bad as death.

Results: Treating all patients with PSG minimized expected health losses, resulting in 475.3 death-equivalents over 25,000 person-years of treatment. Monitoring increased expected health losses by 5 and treating all patients with CPG increased losses by 46.4. Monitoring became dominant when the weight assigned to GI bleeding was increased to 28% or when PSG and CPG were assumed to be equally effective. When uncertainty surrounding PSG's relative efficacy was incorporated through Monte-Carlo simulation, monitoring on average increased expected health losses by 4.8 death-equivalents, but a reduction in health losses from monitoring was supported within the bounds of uncertainty (95% CI: -0.6 to 11.9).

Conclusions: The proposed approach provides a way of integrating expected health harms and benefits of monitoring in the decision to raise a safety alert.

700. Prevalence of PDDI Prescriptions in Two Italian Regions

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Background: Drug-drug interactions are a concern for patients and providers: multiple medication use is becoming more common, with increased risk of untoward effects and drug-related morbidity and mortality.

Objectives: To estimate the prevalence of prescriptions of relevant "potentially interacting drugs" in two Italian Regions and to examine possible predictors of potential drug-drug interaction (pDDI) exposure.

Methods: We retrospectively analysed data on drug prescriptions dispensed from 1 January 2004 to 31 August 2005 to individuals registered under the Regional Health Authorities of two Italian Regions with a population of almost 2.1 million individuals. We identified 27 couples of potentially interacting drugs, by clinical relevance, documentation and volume of use in Italy. Subjects who received at least 1 prescription of both drugs were selected. Co-prescribing was "two prescriptions in the same day"; concomitant medication was "the prescription of two drugs with overlapping coverage". A logistic regression analysis was conducted to examine predictors of pDDIs.

Results: 957,553 subjects (46.0% of study population) were exposed to at least 1 of the drugs/classes of the 27 pairs. These pDDIs occurred 2,465,819 times (Σ of the number of concomitant prescriptions). The most common pDDI was warfarin + NSAIDs (12,492 subjects; 7,581 with concomitant prescription and 2,804 with co-prescriptions). Considering concomitance, males/females ratio was >1 in 10/27 pairs of drugs (from 0.31 for NSAIDs-ASA + SSRI to 0.74 for omeprazole + clopidogrel). Mean age was lowest for methotrexate pairs (+omeprazole, 59.9 years ; +NSAIDs-ASA, 59.1 years), and highest for digoxin + verapamil (75.4 years). In 13/27 the mean ages were ≥70 years. All subjects involved in pDDIs received several drugs during observation (≥10 drugs in 35/27 pairs). Odds of exposure were generally highest for age ≥65 years, male gender, and higher number of drugs.

Conclusions: A substantial number of clinically important pDDIs were identified, particularly among warfarin users. Awareness of the most prevalent pDDIs can help practitioners in preventing concomitant use, thus ameliorating quality of drug prescription and potentially avoiding unwanted side effects.

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701. The Effect of Copayment on Antiretroviral Medication Adherence for Newly Treated HIV-Positive Adults with Commercial Insurance

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Background: Antiretroviral (ARV) therapy is highly effective in reducing morbidity and mortality among HIV-positive patients. Adherence to therapy is an important component of effective treatment. We examined trends in initial antiretroviral usage in a large commercial claims database from 2000 to 2009, as well as the association between antiretroviral copayment and treatment discontinuation.

Objectives: To determine initial ARV usage in a commercial claims database over calendar time, as well as the association between ARV copayment and treatment adherence.

Methods: We created a cohort of new users of antiretroviral drugs in the MarketScan commercial claims database. Initial treatment copayment was our exposure, defined as the total copayment for all drugs within a 14 days window of the first drug prescribed. Treatment discontinuation was our outcome, defined as a gap of 15 days from the end of the previous prescription. We used graphical methods to explore trends in ARV usage. To assess the effect of copayment upon ARV adherence, we used Kaplan-Meier methods and Cox proportional hazards regression to determine the time to treatment discontinuation.

Results: We identified 16,605 new users of ARVs. from 2000 to 2009. The median age was 41 (Interquartile range: 34, 49), 25% of the cohort was female, and the median initial copayment was $40 (IQR: $20, $75). Non-nucleoside reverse transcriptase inhibitor-based therapy was the most prevalent type of initial ARV regimen in the cohort through the study period, comprising 40% of regimens in 2009. We found a small effect of initial treatment copayment for patients with very high copayments over $90, with an adjusted hazard ratio of 1.13 (95% confidence interval: 1.06, 1.20).

Conclusions: We found a small increased hazard of treatment discontinuation among patients with initial copayments over $90, in a large cohort of ARV new users with employer-sponsored commercial insurance. These results suggest that very high copayments for ARV medications could both lead to greater morbidity and mortality for HIV-positive patients as well as higher healthcare costs for both patients and payors.

702. Patient-Reported Reasons for Discontinuation of Commonly Used Treatments for Moderate to Severe Psoriasis

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Background: Despite numerous treatment options with established efficacy and safety, studies on treatments for moderate to severe psoriasis found widespread treatment dissatisfaction and low treatment persistence. Patients' reasons behind treatment discontinuation are poorly understood.

Objectives: To characterize patient-reported reasons behind discontinuing commonly used treatments for moderate to severe psoriasis in real-world clinical practice.

Methods: As part of a multi-center, cross-sectional comparative effectiveness study in 10 dermatology sites across the US, patients with psoriasis who receive, received, or are eligible for systemic treatments completed a structured patient interview at a routine clinical visit. Treatment history was obtained in detail. Eleven reasons for treatment discontinuation, defined *a priori*, were assessed for all past treatments and compared using χ^2 tests.

Results: Of 1,775 patients (95% response), 1,095 reported past use of ≥1 commonly used treatment for plaque psoriasis, totaling 2,231 past treatments. Median treatment duration varied by treatment ($p < 0.001$), ranging from 20.5 months for etanercept to 6 months for acitretin, cyclosporine, psoralen-ultraviolet A (PUVA) and ultraviolet B (UVB). The frequency of citing each discontinuation reason differed by treatment ($p < 0.01$ for each reason). The most common reason for stopping methotrexate (28.3%), acitretin (36.3%), cyclosporine (28.5%), and infliximab (24.2%) was non-life threatening side effects; etanercept was loss of efficacy (32.1%); adalimumab was lack of efficacy (34.0%); PUVA was inconvenience (23.7%); and UVB were clinical improvement and inconvenience (30.5% each). Of note, inability to afford treatment was cited by 11.5% of patients treated with UVB phototherapy, compared to ≤6.0% in other therapies ($p < 0.001$).

Conclusions: Perceived inefficacy and side effects are the main reasons behind treatment discontinuation. Inconvenience and cost may also discourage UVB phototherapy use. These results may inform the development of adherence-promoting strategies that target unmet patient needs.

703. Difference in Persistence Rates between Responders and Non-Responders to Mailed Questionnaires

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Background: Nonpersistence with chronic drug therapy is an important cause of failure of drug therapy. A pitfall in prospective observational studies on medication adherence is selection bias when non-adherent patients do not participate in studies.

Objectives: To investigate whether non-response to mailed questionnaires is associated with nonpersistence.

Methods: In a prospective follow-up study, patients were included in nine pharmacies in The Netherlands and were eligible for inclusion if they filled a first prescription for a drug intended for chronic use: statin, cardiovascular drug, bisphosphonate, antidepressant, or oral antidiabetic drug. All patients received a questionnaire concerning their beliefs about medicines as well as their satisfaction about the information on medicines. Questionnaires were mailed at the time of the first prescription (t0). Electronic dispensing records were extracted from the pharmacies 10 months after inclusion. Nonpersistence was defined as having at least a 60-day gap in the availability of medication. A Cox proportional hazards model was used to evaluate the association between response and persistence.

Results: Of the 355 eligible patients, 178 (50%) responded by sending in the questionnaires. The mean time in which a questionnaire was returned was 19 days. Nonpersistence was 33% in responders and 55% in non-responders. The hazard ratio for non-responders to become nonpersistent was 1.9 (95% CI: 1.3–2.6) compared to responders. Response time was not associated with nonpersistence.

Conclusions: Responders to a mailed questionnaire showed better persistence. Researchers should take this selection bias into account in observational studies on medication adherence. Healthcare workers should focus on non-responders to improve persistence.

704. Real-Life Treatment Persistence with Golimumab (GLM), Etanercept (ETA), and Adalimumab (ADA) in Patients with Rheumatoid Arthritis in Canada

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Background: Tumor necrosis factor-alpha (TNF-α) inhibitors are effective for the treatment of moderately to severely active rheumatoid arthritis (RA), all with similar efficacy at reducing active inflammation and minimizing joint damage. RA is a chronic, life-long disease which requires continuous drug treatment for preventing disease progression. Information on persistence, as a composite outcome for effectiveness and tolerability, with TNF-α inhibitors in clinical practice is limited.

Objectives: The purpose of this study was to examine persistence with TNF-α inhibitors among RA patients in real-life practice in Canada.

Methods: A retrospective cohort analysis was performed using the IMS Brogan private drug plans database in Canada. The study timeframe was from January 1, 2009 to June 30, 2010. Patients were included if they had ≥3 claims for GLM, ETA, and ADA between January 1, 2009 and December 31, 2009. The 6-month period preceding the first claim (index date) was used as a baseline to determine prior biologic use. Utilization patterns and persistence to therapy were assessed 12 months post treatment initiation. The average weekly dose of each drug was evaluated. Persistence was defined as a continuous treatment with consistently refilling a new prescription within 60 days of a previous dispensing.

Results: A total of 146, 1,436 and 1,171 RA patients receiving at least three prescriptions of GLM, ETA and ADA were identified, respectively. The GLM group had a higher persistence rate compared with the ETA and ADA groups (66.4% vs. 55.6% and 59.4%, respectively; $p < 0.05$). The average weekly dose of GLM, ETA and ADA were 11.9, 46.7 and 19.4 mg, respectively, which corroborates their respective label for the treatment of RA in Canada.

Conclusions: This cohort analysis demonstrated that (1) the use of GLM in bio-naïve RA patients is in accordance with the approved monthly dose of 50 mg; and (2) the 12-month persistence to therapy was higher for GLM compared to ETA and ADA in real-life clinical setting. This is the first time that GLM drug utilization pattern in comparison to ETA and ADA is reported in real-life clinical practice.

705. Determinants, Pattern and Outcomes of Non-Adherence to HAART in a Portuguese Cohort of HIV-1 Infected Subjects

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Background: Patient adherence to Highly Active Antiretroviral Therapy (HAART) is a major determinant of clinical success, with impact at healthcare utilization. It is recognized that effective interventions require local assessment of adherence determinants and patterns.

Objectives: To identify determinants of non-adherence to HAART in 2008 year, to characterize frequency and duration of medication gaps and to verify the association

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of non-adherence with immunological and virological outcomes, among HIV-1 infected adults.

Methods: A random sample was selected from all 2,861 HIV-1 adult infected subjects followed up at a HIV outpatient clinic of the largest Portuguese hospital and having at least one HAART refill between 01-01-2005 and 31-12-2008. Average adherence was estimated as medication possession ratio (MPR), with non-adherence defined as MPR < 95%. Viral load (VL), CD4 cell count, and other information on adherence determinants were assessed from clinical records. Bivariate analyses were used to compare the proportion of subjects with VL > 40 copies/mL and CD4 < 350 cells/μL, assuming non-adherence as a dichotomised variable and $\alpha = 0.05$. A multivariate logistic regression model was performed to assess non-adherence predictors.

Results: From the 157 included subjects, 74.1% had MPR≥95% from which 81.6% had more than one medication gap <30 days. Having periods >12 months without medical appointments previous to baseline and ≤3 years of HAART experience were significantly associated to non-adherence. There was a significant decrease in the proportion of subjects with CD4 < 350 cells/μL ($p < 0.001$) and VL > 40 copies/mL ($p = 0.008$), with the increase of the average adherence. Having >3 years of HAART experience and AIDS classification at diagnosis were also associated to virological ($p < 0.001$ and $p = 0.02$) and immunological ($p = 0.05$ and $p = 0.01$) outcomes.

Conclusions: Subjects with less HAART experience and those that had already abandon medical appointments for a period >12 months are more likely non-adherents. Lower to moderate average adherence levels and shorter HAART gaps are frequent among HIV-1 infected adults.

706. Twelve-Year Trend in Treatment Seeking for Buprenorphine, Heroin and Amphetamine Abuse in Finland

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Background: Buprenorphine abuse has become increasingly common worldwide since the 1980s. However, large-scale long-term studies comparing treatment seeking for buprenorphine abuse to treatment seeking for other drug abuse are lacking.

Objectives: This study describes the characteristics of persons seeking treatment for buprenorphine abuse in Finland between 1997 and 2008, and compares these characteristics to those of persons seeking treatment for heroin and amphetamine abuse.

Methods: A 12-year descriptive study was conducted at the Helsinki Deaconess Institute (HDI) in Finland. All persons seeking treatment from the HDI between 31 January 1997 and 31 August 2008 and who reported that their primary drug of abuse was buprenorphine (n = 780), heroin (n = 598) or amphetamine (n = 1,249) were included. Structured clinical interviews concerning clients' demographic characteristics and abuse patterns were conducted by specialist nurses and physicians.

Results: The proportion of clients seeking treatment for buprenorphine abuse increased from 3.0% in 1998 to 38.4% in 2008. Concurrent abuse of prescription medications ($p < 0.001$), stimulants ($p = 0.001$) and alcohol ($p < 0.001$) increased during the study period. Treatment seeking for heroin abuse declined to approximately 1% of clients after 2002. Buprenorphine clients were more likely to be daily users of their primary drug of abuse compared to heroin ($p = 0.022$) and amphetamine ($p < 0.001$) clients. Intravenous (IV) administration was more common among buprenorphine clients compared to heroin ($p < 0.001$) and amphetamine clients ($p < 0.001$ in 1997–2001).

Conclusions: Our results highlight the increasing abuse of buprenorphine in Finland. Buprenorphine clients have more risky abuse patterns compared to heroin and amphetamine clients in terms of IV administration and daily use. Concurrent substance abuse increased during the study period.

707. Propensity Scores in Sequential Monitoring of New Drugs: Evaluation of Dynamic Matching

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Background: Propensity scores (PSs) offer many benefits for confounding control in sequential analyses. However, determinants of drug use evolve rapidly in the early marketing period and little is known about how best to estimate and use PSs in this setting.

Objectives: To compare two approaches to PS matching in sequential analyses. In both cases, a cohort is built sequentially as new data accrue, and PSs re-estimated at each data update. One approach (fixed matching) involves fixing matches at the time that they are created and the other (dynamic matching) allows patients to re-match using the most current PS estimate.

Methods: In US Medicare data, we compared the approaches in a study that mimicked sequential monitoring of two antibiotics, telithromycin (T) vs. azithromycin (A), on risk of hepatotoxicity. We divided data into 10 time periods beginning at T's launch. We estimated the PS using data from the first period and re-estimated it nine times by adding data from subsequent periods. In the fixed matching approach, we matched patients within each new period without disturbing prior matches. In dynamic matching, we allowed all patients to re-match, within each period, each time the PS was re-estimated. We evaluated the proportion of telithromycin patients matched and the number of outcomes in each matched group over time, and used a summary distance measure to compare period-specific confounder balance between treatment groups in each approach.

Results: Over the 10 periods, we identified 53,296 A users and 4,005 T users. Dynamic matching resulted in an equal or higher proportion of T users matched in all periods (99.6% vs. 98.4% overall). This proportion increased monotonically for both approaches, but re-matching resulted in a fluctuating number of events among matched A users over time. Dynamic matching resulted in better confounder balance in 52% of periods. Effect estimates did not materially differ between the approaches.

Conclusions: As compared to keeping prior matches, re-matching patients in sequential analyses may complicate alerting algorithms by inducing variability in the number of observed outcomes over time without the added benefit of attaining better covariate balance.

708. Value of Disease Risk Scores in Comparative Effectiveness Research with Emerging Therapies

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Background: Use of a propensity score (PS) to balance potential confounders at treatment initiation may be limited for newly introduced therapies with evolving use patterns, as early adopters may differ from later users of the therapy. In this setting, the disease risk score (DRS) has theoretical advantages as a balancing score in comparative effectiveness research, because of stability of disease risk and the presence of ample historical data on outcomes in people treated before availability of the new therapy.

Objectives: We discuss principles in the construction of a DRS, and its balancing properties. We consider alternative study designs including control for a DRS in a multivariable model, matching solely on the DRS, jointly on this score and a PS, and use of time-varying weights, with the DRS weighed more heavily in early follow-up and a time-varying PS weighed more in later follow-up.

Methods: We illustrate development of a DRS and alternative designs in the context of the introduction of atorvastatin and the use of high-dose statin therapy beginning in 1997, based on data from 5,668 older survivors of myocardial infarction who filled a statin prescription within 30 days after discharge from 1995 until 2004. The study outcome was recurrent myocardial infarction, stroke, or death within 1 year.

Results: Theoretical considerations suggested the development of a DRS among non-users of atorvastatin and high-dose statins during the period 1995–1997. Observed risk of events increased from 11% to 35% across quintiles of the score, suggesting its potential value as an axis for evaluation of effect modification. Development of a PS in early follow-up (e.g., 1997–1998) was limited by a small number of users of high-dose statins in that period. Time-specific PS models showed evidence of over-fitting, and variability in coefficients over time. Both stratified analyses and multivariable models adjusted for DRS suggested small reductions in risk associated with use of atorvastatin (OR 0.93; 95% CI: 0.81–1.07) and high-dose statins (OR 0.94; 95% CI: 0.79–1.12).

Conclusions: Balancing on a DRS offers an attractive alternative to the PS in some settings such as newly marketed drugs.

709. The Power of Electronic Healthcare Databases for Active Drug Safety Surveillance in Children and Adolescents: An EU-ADR Study

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Background: Traditional pharmacovigilance activities do not focus on children and medicines are frequently being used off-label based on extrapolating experience from adults. Various initiatives in USA and Europe are cur-

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rently exploring whether mining of electronic health care records (EHR) can complement existing spontaneous reporting systems. None of these initiatives so far has looked specifically at children.

Objectives: To provide estimates of the number of drugs and event rates that can be monitored in children and adolescents in the EU-ADR database network.

Methods: A cohort study was performed using data from seven population-based EHR databases of the EU-ADR network in three countries (1996–2008). We estimated the number of drugs that can be monitored based on the amount of drug exposure required for empirically-derived IRs for 10 events of interest across varying magnitudes of relative risk (RR). The same was done for events frequently occurring in children using IRs from literature.

Results: The paediatric cohort (0–18 years) comprised 4.8 million individuals contributing 25.6 million personyears (PYs) of follow-up. Of the total 2170 drugs (total exposure 1.6 million PYs), 18 drugs (0.8%) made up 50% and 158 drugs (7.3%) made up 90% of the drug exposure in PYs. For a frequent event like upper gastrointestinal bleeding (IR = 14.4/100,000PYs), 39 drugs (66% of exposure) had enough exposure to investigate an association with RR≥4. For rare events like anaphylactic shock or bullous eruptions there were 8 (35% of exposure) and nine drugs (37% of exposure) respectively for which an association of same magnitude can be investigated. Based on literature-derived IR, there was a higher number of drugs that can be monitored for the events febrile convulsions, suicide attempt and epilepsy.

Conclusions: Drug use in children is rare, only 18 out of the 2,170 prescribed drugs make up half of the total exposure time to drugs. The number of drugs with enough exposure to monitor drug safety within EHRs for rare events in paediatrics is limited. For paediatric drug safety monitoring with EHRs global approaches seem necessary to have enough power.

710. An Application of Univariate Self-Case Control Series Method Using THIN Database in the OMOP CDM for Active Drug Safety Surveillance

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Background: The Observational Medical Outcome Partnership (OMOP) has conducted methodological research to assess feasibility and applicability of active surveillance methods including Univariate Self-Case Control Series (USCCS) using various US observational databases.

Objectives: To test the USCCS method using UK THIN Database mapped into OMOP Common Data Model (CDM) and assess performance characteristics.

Methods: We applied the SAS codes and parameter settings of USCCS method provided by OMOP to the CDM THIN. Drug of Interests (DOI) and Health of Outcome of Interests (HOI) predefined by OMOP were used as exposures and outcomes. Fifty-three drug-outcome pairs assessed by OMOP for true associations (nine positive pairs and 44 negative control pairs) were used as a reference set for comparison.

Results: USCCS method can highlight true associations: all nine pairs considered true positive sets by OMOP had relative risk (RR) >1 and at least seven pairs demonstrated statistical significance ($a = 0.05$) in each of 4 surveillance windows (SW = -30, 0, 30, and 60 days). Overall false positive rate, ranged from 41 to 64%, varies by the selection of SW. However $>70\%$ of false positive pairs had RR <2. Changing the parameter settings from first to all occurrences and varying the four precision levels had little impact on the results. Changing the exposure start date from day 1 to day 0 produced far more false positive pairs. Variability in the identification of true negatives, when using multiple definitions of HOI, was observed. Compared to Proportional Reporting Ratio method, USCCS had better performance in highlighting the true association known by OMOP in CDM THIN.

Conclusions: USCCS method implemented in an automated manner for open ended surveillance can highlight known safety issues in CDM THIN with a false positive caveat. Method performance is sensitive to the selection of risk period and exposed time at risk, but less sensitive to the choice of precision level and first vs. all occurrences. A RR <2 may incur higher rates of false positives. Further research on SCCS including determining an appropriate threshold for signal detection is essential.

711. Trends in Medication and Survival Following an Acute Myocardial Infarction in Primary Care in the UK – Re-Analysis of THIN Database with OMOP Common Data Model

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Background: The Observational Medical Outcome Partnership (OMOP) provides a common data model (CDM) to standardize structure of electronic medical databases and test different methods of pharmacoepidemiology research across different databases. We have converted the Health Improvement Network (THIN) database into the OMOP CDM, and performed extensive assessment of internal validity.

Objectives: To further assess validity and value of CDM THIN by re-analysis of an independent peer reviewed study performed on raw THIN database and comparing the results.

Methods: With CDM THIN, we repeated the analysis of Hardoon et al. published on *J Epidemiol Community Health* in 2011. The same inclusion/exclusion criteria used in the publication were applied to create a cohort of MI patients who were 35 years or over at the time of MI diagnosis, and who survived for at least 3 months after the MI. With this cohort, the rate of death from 3 months to 3 years after the first MI was estimated. We also analyzed prescribing of lipid-regulating drugs, beta-blockers, ACE inhibitors and anti-platelet medications in the 3 months following the MI during the year 1991 to 2002.

Results: The comparison between CDM THIN and Hardoon's paper revealed that the cohort from the CDM THIN has the same gender distribution as the article (64% male) but slightly younger age (mean age 66.7 vs. 67.9). The death rate from CDM THIN analysis was slightly higher than the published result, but the time trend from the two analyses was comparable. For the medication after MI diagnosis, our analysis shows that the prescription rates of all four drugs within 3 months of MI increased over time, and the patterns were almost identical to the published results.

Conclusions: With the CDM THIN, we were able to quickly replicate the conclusion that the death rate after the first MI diagnosis decreased during the 10 years from 1991 to 2002, and this decrease was associated with the increased use of the four drugs. The results provides more evidence that the CDM THIN is valid and might be applied to improve efficiency of pharmacoepidemiological research.

712. PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) Work Package 6: Project Synthesis

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Background: PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) consists of 29 public and private Partners coordinated by the European Medicines Agency (EMA). Within this framework, Work package 6 (WP6) has been developed to test the transferability/feasibility of methods developed in WP2 to 5 in a range of data sources. These methods will be tested in real-life situations in order to provide all stakeholders with accurate and useful information supporting risk management and continuous benefit-risk assessment.

Objectives: The aims of WP6 are to assess the following scientific questions: is a study replicable when conducted independently in the same database? Do the results have external validity? Does a study using the same protocol provide no evidence of association where the exposure is such that the expected result is one of no association? What is the impact of different levels of certainty of the outcome on the effect estimate? Has an outcome been validated through clinical record review and does this validation impact on the effect estimate? Has confounding been adequately taken into account? How does better control for confounding impact on the effect estimate?

Methods: In February 2012, WP6 has established an extended group of data partners and identified data bases for the following outcomes of interest which are based on the primary adverse event – drug pair groups in WP2: use of inhaled beta-2 agonists and acute myocardial infarction; use of antibiotics and drug induced liver injury; use of antidepressants or benzodiazepines and hip fracture; use of anticonvulsants and suicide/suicide attempt; use of calcium channel blockers and malignancies and finally use of antibiotics and myocardial infarction for a negative-control validation study.

Results: This work will provide a systematic approach to evaluating some of the relevant methodologies in WP2 using alternative data sources.

Conclusions: Wide and proactive dissemination of the results of WP6 should ultimately bring maximum benefits to patients; and the presence of patients' associations as Partner and Member of the External Advisory Board will help achieve this objective.

713. Was the Use of Antipsychotic Drugs with Arrythmogenic Potential Changed in the Last Years? A Population-Based, Database Study in five European Countries

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Background: Several antipsychotics are associated with an increased risk of QT prolongation, potentially leading to Torsades de Pointes (TdP) and Sudden Cardiac Death (SCD). In 2005, thioridazine was withdrawn from the market because of SCD risk, thus further raising the attention of scientific community about the arrhythmogenic potential of antipsychotics.

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Objectives: To evaluate the yearly trend in use of antipsychotic drugs in relation to TdP liability in five European Countries during the years 1996–2010.

Methods: A cross-sectional study was conducted using prescription/dispensing data from six healthcare databases (AARHUS, GEPARD, HSD, ERD, PHARMO and THIN), covering a population of 27 million individuals. For each study year, the prevalence of antipsychotic drug use, overall and stratified by drugs with established and possible TdP risk, according to ArizonaCERT list, was measured. Drug consumption was expressed as the number of defined daily doses per 1,000 inhabitants/day (DDD/1,000 Inh/day). All the analyses were stratified by age, gender, and calendar year.

Results: The overall prevalence of antipsychotic drug use was rather comparable across different databases, ranging from 3.0/1,000 PYs in ERD to 7.7/1,000, PYs in AARHUS. A total amount of 551,490 PYs of exposure to antipsychotic drugs was captured in the six databases, with drugs with TdP liability accounting for 35.7% of this amount. Among drugs with established TdP liability, haloperidol was the most frequently prescribed compound in all DBs, while risperidone was the most commonly used antipsychotic among drugs with possible TdP liability. As for other antipsychotics, those with TdP liability were much more prescribed in patients older than 65 years. The trend in the use of antipsychotics with TdP liability was rather stable after withdrawal of thioridazine.

Conclusions: Large use of antipsychotic drugs with TdP liability was reported in the last years in the European countries, despite increasing concerns about their arrhythmogenic potential. This use was even greater in elderly patients who are at higher risk of SCD, thus requiring careful monitoring.

714. The Risk of Antipsychotic-Induced Parkinsonism and Its Management

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Background: Despite safety warnings, antipsychotic medications (APMs) are still used widely for behavioral problems in dementia. Atypical APMs are less likely than older agents to produce extrapyramidal (parkinsonian) symptoms (EPS), but the risks of individual drugs in routine care have not been assessed.

Objectives: To compare the risk of EPS in older adults taking specific APMs, and to evaluate subsequent regimen changes.

Methods: Cohort study of 49,050 adults ≥65 years who began an APM (36,559 atypical and 12,491 typical agents), did not have a schizophrenia or bipolar diagnosis, were enrolled in Medicare and received drug coverage through a state-based or private insurer between 1995 and 2008. We used Cox proportional hazards models to study the development of EPS as indicated by a new ICD-9 diagnosis or antiparkinsonian drug use over 1 year. We used propensity score adjustment to control for confounding.

Results: 3.7% of new APM users developed EPS during the first year of follow-up. Relative to risperidone users, those taking haloperidol were twice as likely to develop EPS (adjusted hazard ratio = 2.10; 95 % CI 1.83–2.42). Patients prescribed ziprasidone (1.59; 95% CI 1.05–2.41) and aripiprazole (1.47; 95% CI 1.12–1.93) were at greater risk, olanzapine users were at similar risk (0.92; 95% CI 0.79–1.07), and quetiapine users were at lower risk (0.78; 95% CI 0.67–0.91) of newly diagnosed or treated EPS relative to risperidone users. Within 90 days of the first EPS diagnosis or treatment, APM use remained unchanged for 46.4% of patients, and 8.6% had their dose increased. Among patients taking an atypical APM who were prescribed an antiparkinsonian drug, 45.3% were given a dopaminergic drug specific for idiopathic Parkinson's disease, compared to only 8.6% of typical APM users.

Conclusions: These findings document a differential risk of parkinsonian symptoms for specific APMs and are consistent with the drugs' pharmacological profile, except for aripiprazole. The widespread initiation of added dopaminergic drugs to treat this adverse effect and the frequency of continued or increased APM use thereafter, suggest that many physicians are not aware that these symptoms may be drug-induced.

715. Anti-Dementia Drugs in Patients with Alzheimer's Disease and the Risk of Developing Seizures or Epilepsy: A Population-Based Nested Case–Control Analysis

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Background: Several epidemiological studies have shown that patients with Alzheimer's disease (AD) have an increased risk of developing seizures or epilepsy. However, little is known about the role of specific anti-dementia drugs such as acetylcholinesterase inhibitors or memantine, but these drugs have been reported to rarely provoke seizures.

Objectives: To explore the role of specific anti-dementia drugs such as acetylcholinesterase inhibitors or memantine on the risk of developing seizures or epilepsy in patients with AD.

Methods: We conducted a follow-up study with a nested case–control analysis using the UK-based General Practice Research Database (GPRD). The study population consisted of patients aged ≥65 years with an incident diagnosis of AD between 1998 and 2008 and a matched comparison group of dementia-free patients. Conditional logistic regression was used to estimate the odds ratio (OR) with 95% confidence intervals (CIs) of developing seizures or epilepsy in patients with AD, stratified by use of anti-dementia drugs and adjusted for various potential confounders.

Results: Within the study population of 19,227 patients we identified 128 cases with an incident diagnosis of seizures or epilepsy. As compared to patients without dementia, the adjusted ORs of developing seizures or epilepsy in patients with AD not receiving any anti-dementia drugs was 5.56, 95% CI 3.27–9.47 and 6.19, 95% CI 3.59–10.69 in those treated with anti-dementia drugs. A further stratification into users of acetylcholinesterase inhibitors or memantine only was not meaningful due to the small number of memantine users.

Conclusions: In our study population, the risk of developing seizures or epilepsy in patients with AD was substantially higher than in non-demented patients. However, the risk was similarly increased regardless of whether patients took anti-dementia drugs or not.

716. Comparative Cardiovascular Safety of Dementia Medications: A Cross-National Study

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Background: Little is known about the cardiovascular safety profiles of dementia medications.

Objectives: To assess the comparative cardiovascular safety of currently marketed dementia medications in the US Medicare population and in Denmark

Methods: Using a nationally representative 5% sample of US Medicare beneficiaries from 2006 through 2009 and nationwide administrative registries in Denmark from 1997 through 2007, we identified new users of dementia medications aged 65 years or older. We examined the following cardiovascular safety outcomes associated with the use of these drugs: hospitalizations for myocardial infarction (MI), heart failure (HF), and syncope or atrioventricular (AV) block in both cohorts; and fatal or nonfatal MI and cardiac death in the Danish cohort only. We calculated all-cause mortality in sensitivity analyses. We used Cox proportional hazards models to compare cardiovascular risks, using donepezil as the reference category.

Results: Among 46,737 Medicare beneficiaries and 29,496 Danish patients, donepezil was the most frequently used dementia medication. Compared with donepezil, there were no substantial differences in the risk of MI, HF, or syncope or AV block among patients using other cholinesterase inhibitors. Hazard ratios for the composite outcome of MI, HF, or syncope or AV block were 0.73 (95% CI, 0.51–1.05) and 0.99 (0.86–1.15) for galantamine and 0.93 (0.77–1.12) and 1.12 (0.94–1.33) for rivastigmine. However, in the Danish cohort, memantine was associated with greater risks of MI (1.33; 1.08–1.63) and cardiac death (1.31; 1.12–1.53). Memantine was also associated with greater risk of all-cause mortality. The smaller increase in risk in the Medicare cohort (1.20; 1.13–1.28) and the larger effect in the Danish cohort (1.83; 1.73–1.94) suggests selection of sicker patients for memantine in the latter cohort.

Conclusions: The cholinesterase inhibitors have similar cardiovascular risk profiles. Observed associations between memantine and fatal outcomes in Denmark may be related, in part, to selection of sicker patients for memantine therapy.

717. Cardiovascular Outcomes in Patients Using Clopidogrel with Selective Serotonin Reuptake Inhibitors

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Background: Selective serotonin reuptake inhibitors (SSRIs) have been shown to improve motor recovery after ischemic stroke. However, their inhibitory effect on CYP2C19 may impair the bioactivation of clopidogrel, which is often coprescribed for secondary prevention after stroke and acute coronary syndromes.

Objectives: We sought to study the effect of CYP2C19-inhibiting SSRIs on the risk for both ischemic and hemorrhagic events in clopidogrel users.

Methods: We identified cohorts of clopidogrel initiators with concomitant SSRI pharmacotherapy in three US claims databases (Medicare data from two states and data from a large commercial health plan). We compared event rates between users of the CYP2C19-inhibiting SSRIs fluoxetine or fluvoxamine and users of SSRIs with negligible CYP2C19 inhibiton, using a propensity-score adjusted Cox proportional hazards model. We included in the propensity score known risk factors for cardiovascular outcomes and we stratified the Cox model by database.

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Hazard ratios were estimated in intention-to-treat (ITT; up to 180 days) and as-treated (AT) analyses.

Results: Among 2300 eligible patients with SSRI exposure at the time of clopidogrel initiation, 309 (13.4%) used fluoxetine or fluvoxamine. The mean duration of concomitant clopidogrel and SSRI exposure was 28.3 days and was similar between groups. Overall we identified 320 ischemic and 53 hemorrhagic events in the 180 days following clopodigrel initiation. Hazard ratios for ischemic events (95% CI) comparing inhibitory vs. non-inhibitory SSRI users were 1.10 (0.79, 1.52) in the ITT analysis, and 0.99 (0.58, 1.67) in the AT analysis. For hemorrhagic events, hazard ratios (95% CI) were 0.72 (0.31, 1.71) in the ITT and 0.59 (0.14, 2.58) in the AT analysis.

Conclusions: Our results did not indicate a significant effect of CYP2C19-inhibiting SSRIs on the risk of thromboembolic events in clopidogrel users. We observed a reduction in hemorrhagic events, consistent with the hypothesized interaction mechanism, but confidence intervals were wide and the absolute event incidence was low.

718. Use of cetuximab in a real-life setting in France with respect to KRAS status: results of EREBUS cohort study

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Background: Cetuximab demonstrated survival outcome improvement in metastatic colorectal cancer (mCRC). Cetuximab was first launched as a second-line therapy in mCRC. In July 2008, this indication was extended to first-line therapy and restricted to mCRC patients with wild-type (wt) KRAS gene.

Objectives: To describe cetuximab prescription patterns according to KRAS status in a real-life setting.

Methods: EREBUS is a cohort study conducted in 92 French centers. Patients initiating cetuximab between Jan and Dec 2009 were identified from nominative hospital pharmacy dispensations. For all patients identified as new users of cetuximab in CRC, KRAS status as well as reasons for absence of KRAS investigation were collected in patient medical files. KRAS investigation and status were described globally and according to treatment line and stage of CRC.

Results: A total of 1038 patients initiating cetuximab for CRC has been identified between Jan and Dec 2009. Cetuximab was mainly prescribed in mCRC (98.0%): 34.4% as first-line treatment, 34.5% as 2nd-line, 21.4% as third-line and 9.7% as fourth or more. The investigation of KRAS status was performed in 94.4% of the patients and, of these, 94.9% had wt KRAS gene. Investigation of KRAS mutation status and wt status was similar regardless of treatment line (investigation: between 93.3% and 100.0%; wt status: between 93.9% and 100.0%). The investigation was performed on primary tumor (82.6%), on metastases (16.3%) or both (1.1%). The main reasons of absence of KRAS status investigation were: previous treatment by cetuximab (42.9%) and absence of available tumor material or technical issue with analysis (33.3%).

Conclusions: EREBUS is the first post-marketing cohort study conducted in France to describe the usage patterns of cetuximab. Extensive investigation of KRAS status and the high proportion of patients with wt status indicates adherence to market authorization.

719. Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) Initiative

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Background: Guidelines for reporting observational studies (Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were published in 2007. However, we are unaware of any guideline for reporting studies based on routinely collected health data. These studies share many characteristics with traditional observational studies, but specific issues exist which are not covered due to the general nature of STROBE. The international RECORD initiative represents users of primary care databases, insurance claims databases and population-based health registries.

Objectives: To develop a reporting guideline for observational studies using routinely collected health data as a STROBE extension.

Methods: Reporting guidelines for studies conducted using observational routinely collected data will be developed using the 18 stage EQUATOR Network approach (www.equator-network.org/resource-centre/reporting-guidelines-developers). *Stage 1*: An initial workshop was held in London UK in January 2012. To

identify issues specific to reporting from these data a series of meetings and surveys will be held throughout 2012–2014. The RECORD guideline will supplement existing guidelines for observational studies (STROBE).

Results: The workshop included more than 100 participants from Europe and Canada (including five members of the STROBE organizing committee). Participants agreed that reporting of research using routine data sources was often insufficient and highly variable. Potential topics for the RECORD guideline may include description of database characteristics, validation of codes and algorithms to identify exposures and outcomes and record-linkage methodology. To identify further topics for the RECORD guideline, the working group plans two large international Delphi surveys and face-to-face meetings including expert stakeholders, journal editors and guideline developers.

Conclusions: Reporting guidelines specific to studies using routinely collected health data are required. Throughout 2012–2014 the RECORD initiative will extend the existing STROBE statement by developing such a guidance document to be published in high-profile biomedical journals.

720. Development and Validation of a Classification Algorithm for Prophylactic vs. On-Demand Factor VIII Therapy in Patients with Hemophilia A

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Background: Health insurance claims databases are well-suited to study rare diseases such as hemophilia, but lack specific codes for classifying prophylactic (PPL) vs. on-demand (OD) factor VIII (FVIII) regimens in hemophilia A (HA) patients (pts).

Objectives: To develop and validate a classification algorithm to identify PPL vs. OD FVIII regimens in claims databases.

Methods: Prescription records from a 2010–2011 US specialty pharmacy dispensing database were used. Males ≥2 years old with a HA diagnosis, ≥1 prescription for FVIII, no anti-inhibitor agents or mixed PPL/OD FVIII regimens were included. Three common variables in specialty pharmacy and claims databases were used to develop the algorithm:

age at 1st observed dispensing (a weight proxy); vial potency (IU/vial) and # of vials dispensed were used to calculate total units of FVIII (TUFVIII) dispensed (IU/vial*# vials dispensed). Different TUFVIII thresholds per age groups 2–12, 13–16, 17–24, and 25+, and pts' estimated weights formed the algorithm. Several TUFVIII thresholds for each age group were iteratively tested over various observation lengths for pts classified as on PPL (vs. OD) regimen. Each algorithm was assessed against actual regimens prescribed based on physician notes using sensitivity, specificity, positive and negative predictive values (PPV NPV).

Results: Of 172 pts identified, 70% were on PPL regimens. Mean age (years) across OD and PPL cohorts was similar (OD: 23.3 ± 16.2; PPL: 23.7 ± 13.0). Majority of OD pts had mild/moderate HA (65%) vs. most PPL pts had severe HA (88%). The best-performing algorithm was based on TUFVIII thresholds of 49,600 (age group 2–12), 74,400 (13–16), 100,000 (17–24), and 66,000 (25+), over the 1st 5 months of observation. Sensitivity, specificity, PPV, and NPV of this algorithm were 0.86, 0.85, 0.95, and 0.66, respectively.

Conclusions: The best-performing algorithm showed promising performance validity with PPV > 0.90 for ascertainment of PPL FVIII regimens in HA pts. A classification algorithm for identifying PPL vs. OD FVIII regimens among HA pts in claims databases will enable the assessment of these therapies in real-world settings.

721. Is Off-Label Use a Risk Factor for Adverse Drug Events?

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Background: Off-label use has been identified as an important contributor to preventable adverse drug events (ADE) in children. In adults, drugs implicated include fen-phen (valvulopathy), combined estrogen-progestin (breast cancer), and tiagabine (status epilepticus). Despite concerns for adverse outcomes, there has been no systematic investigation of the effects of off-label use in adult population in "real world" setting.

Objectives: To determine the association between off-label use and adverse drug events.

Methods: The MOXXI electronic health record (EHR), which allows documentation of treatment indications and treatment outcomes, was used to assemble a cohort of 46,294 patients who received 153,144 incident drugs between January 2005 and December 2009. Person-time was accrued until the drug was discontinued or the end of follow-up (December 2010). *Outcome*: Adverse drug events (ADE) were defined as drug discontinuations made by physicians due to adverse drug reaction. *Exposure*: Treatment indication recorded for each drug was classified as on- or off-label using Health Canada drug database. *Covariates*: Drug class, drug age, patient age, sex, comorbidity, number of drugs and continuity of care (COC). *Statistical analysis*: Multivariate marginal Cox regression for clustered data where the unit of analysis was drug.

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Results: There were 3,499 ADE with incident rate (IR) of 13.3 per 10,000 person-months. For off-label and on-label uses, the IRs were 19.8 and 12.5 per 10,000 person-months, respectively (HR, 1.43 [95% CI, 1.29–1.59]). Anti-infectives had the highest incidence rate. Patients who had received ≥8 drugs had increased risk of ADE than patients with 1–2 drugs (IR: 19.1 vs. 4.4; HR, 5.77 [95% CI, 4.77–6.97]). Patients in the bottom quartile for age had higher risk of ADE compared to the three older quartiles. Females had higher risk of ADE than males (HR, 1.12 [95% CI, 1.02–1.24]). Drugs approved after 1981 had greater risk of ADE than drugs approved before 1981. A 25% increase in COC increased the ADE detection by 22% (HR, 1.22, [95% CI, 1.12–1.33]).

Conclusions: Off-label use is a risk factor for ADE. Treatment indications and treatment outcomes are essential to monitor the safety of on- and off-label uses of drugs.

722. The Role of Surveillance Bias in the Incidence of the Myelodysplastic Syndromes and Chronic Myeloproliferative Disorders

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Background: Myeloid neoplasms (MNs) are a subset of hematologic malignancies that include myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMPD), and acute myeloid leukemia (AML). MDS and CMPD can be asymptomatic conditions that may be undiagnosed for indeterminate amounts of time, and diagnosis is often made as a result of routine blood tests. We hypothesize that patients receiving more frequent blood tests are more likely to be diagnosed with MDS or CMPD, but not more likely to be diagnosed with AML which has a more acute presentation.

Objectives: To estimate the effect of surveillance bias (routine blood tests) on diagnosis of MDS, CMPD or AML.

Methods: We conducted a nested case–control study using the General Practice Research Database. Incident cases of MNs were identified and up to four controls were matched to each case. Exposure was defined as the number of blood tests performed per year in the 5 years prior to the index date, and also stratified by 0–2 years and 3–5 years prior to the index date. Conditional logistic regression models were used to estimate odds ratios (ORs) to quantify the effect of blood test frequency on the diagnosis of MDS, CMPD, and AML separately.

Results: We identified 185 cases of MDS, 399 cases of CMPD, and 151 cases of AML who met our inclusion criteria. There was an increased risk of MDS and CMPD in patients with at least 5 blood tests over the 5 years period prior to the index date (adjusted ORs 2.4, 95% CI 1.3, 4.5 and 1.6, 95% CI 1.1, 2.5, respectively) as compared with patients with no recorded blood tests. Stratifying on time prior to the index date had no effect. There was no increased risk of AML (adjusted OR 1.1, 95% CI 0.5, 2.3) in patients with at least 5 blood tests over the 5 years period.

Conclusions: Our study is consistent with the hypothesis that diagnosis of MDS or CMPD is subject to surveillance bias while diagnosis of AML is not. The increased risk for MDS and CMPD is present in increased blood test frequency both 0–2 years and 3–5 years prior to the index date, indicating reverse causation is not a likely explanation.

723. Validation of Congenital Cardiac Malformations in the General Practice Research Database

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Background: The General Practice Research Database (GPRD) Mother-Baby Link data show promise in helping researchers assess the associations between medication exposure during pregnancy and congenital malformations.

Objectives: To determine the positive predictive value (PPV) of GPRD Read codes in identifying congenital cardiac malformations.

Methods: We extracted all diagnostic and surgical codes for congenital cardiac malformations from electronic medical records. Those codes were used to identify possible infant cases in our GPRD Mother-Baby Link population, which consisted of 149,464 live-birth singletons delivered between 1996 and 2010 who did not have chromosomal malformations and whose mothers were enrolled in GPRD from at least 15 months prior to conception through delivery. We identified 1024 possible cases of which 888 infants were cared for by General Practitioners (GPs) who currently contribute data to GPRD. Questionnaires were sent to the GPs to validate the diagnosis, and date and method of diagnosis. The PPV of the codes was calculated as the proportion of complete questionnaires in which a cardiac malformation was confirmed (1) by the GP; and (2) by imaging techniques or surgery, as reported by the GP in the questionnaire. A pre-specified PPV threshold of 0.8 was used to determine whether diagnosis based on Read codes is acceptable.

Results: We received 716 completed questionnaires (response rate = 80.6%). We eliminated 22 duplicate questionnaires leaving a total of 694 possible cases. A total

of 633 cases were confirmed, of which 569 were confirmed by record of imaging techniques or surgery. The corresponding PPVs. and 95% confidence intervals were 0.91 (0.89–0.93) and 0.82 (0.79–0.85) respectively.

Conclusions: GPRD Read diagnostic and surgical codes are sufficient to identify congenital cardiac malformations without the need for additional validation via GP questionnaire response.

724. Development of a New System for Registration of Patient Registries

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Background: Patient registries are an important tool for clinical research, including comparative effectiveness research (CER), but there is no central database designed specifically to list patient registries. A searchable public database that is designed specifically to provide information about patient registries would support research collaborations, reduce redundancies, encourage the efficient use of resources, and improve transparency in CER and other types of observational clinical research.

Objectives: The goal of this project, funded by the Agency for Healthcare Research and Quality, is to design and develop a Registry of Patient Registries (RoPR) system that meets the needs of multiple stakeholders.

Methods: Stakeholders from a broad range of organizations and with varying levels of familiarity with patient registries were invited to participate in a series of meetings to gather and refine the RoPR system requirements. Requirements were also revised through public comment periods and usability testing.

Results: Over 320 individuals participated in RoPR requirements gathering activities. Participants represented funding agencies (n = 48), government regulatory or public health agencies (n = 13), industry (n = 78), journal editors (n = 6), patient/consumers (n = 30), payers (n = 8), providers or physician associations (n = 49), researchers (n = 79), and other (n = 21). Based on stakeholder feedback, it was determined that the RoPR will be integrated with ClinicalTrials.gov and will collect information on registry purpose, objectives, data collection, recruitment and follow-up, analysis plans, quality procedures, and interest in collaboration and/or data sharing opportunities.

Conclusions: The RoPR, which launches in September 2012, will be a publically available, searchable website designed specifically for listing patient registries. The information collected in the RoPR will enable RoPR users to identify registries in which they may wish to participate or that may be suitable for collaborative projects, such as data linkage or embedded studies. By incorporating stakeholder feedback throughout the design and development process, it is hoped that the RoPR will meet the needs of multiple, diverse stakeholder groups.

725. Electronic and Personal Health Records: Utility and Challenges for Comparative Effectiveness Research (CER)

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Background: Rising adoption rates of health information technology (HIT) such as electronic health records (EHRs) and personal health records (PHRs) have resulted in increased opportunities and interest in using this technology for research. EHRs and PHRs can be rich sources for CER but researchers need to be aware of their limitations and of newer techniques if their advantages are to be maximized.

Objectives: To review the current state and potential of HIT for CER and to discuss technical and methodological considerations when using this technology to conduct medication and medical device CER using ongoing or recent studies as cases.

Description: We will have a series of didactic presentations (followed by question and answer periods moderated by MCJMS and ESJ) covering the nature, promise, limitations, and data extraction techniques for EHRs and PHRs in the context of CER. Real-world examples will be drawn from (1) an AHRQ-funded project comparing the effectiveness of carotid revascularizations relative to medical therapy; (2) a pan-European project using text mining to identify outcomes in general practice databases; and (3) a pilot project assessing patient-reported-outcomes (PROs) using PHRs.

The session will feature the following topics and presenters (shown by initials): 1. Overview: Broad overview of the different types of electronic health data useful for CER, including a discussion of US privacy and security concerns and HIPAA issues related to use of these data for research (SLW).

2. EHRs and Imaging Data for CER: Discussion of challenges to applicability of EHRs for CER including lack of standardization and limitations relating to data quality, missingness, censoring and generalizability (JJJ).

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3. Text Mining: Discussion of some of the most promising text mining techniques to extract data from EHRs and their applicability to CER, using several real-world examples (MJS).

4. PHR for CER, a new horizon: Discussion of a pilot survey using PHRs to capture PROs after device implantation and of the potential utility of PHRs for post-marketing surveillance of medications and implanted devices (SS).

726. European Initiatives To Study Adverse Events of Treatments for Diabetes Mellitus

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Background: In recent years, several diabetes treatments have been associated with serious adverse events. Glitazones have been associated with an increased risk for cardiovascular outcomes, and the marketing authorization of rosiglitazone has been suspended as a result. In addition, several diabetes treatments have been associated with cancer; pioglitazone may cause bladder cancer, and insulin analogues may increase the risk for breast cancer. As a result, adverse events of anti-diabetic drugs are one of the main challenges drug regulators are dealing with nowadays. Because discussions on the causality are still ongoing, several projects have been initiated to study adverse events of treatment for Diabetes Mellitus.

Objectives: In this symposium, principal investigators of several European research initiatives on adverse events of treatment for Diabetes Mellitus will present their studies. Both industry funded and researcher initiated, as well as EU-FP7 consortia will be represented. A special focus is on methodological issues that are specific for studying adverse drug reactions in a diabetic population, such as confounding by underlying disease severity, adjustment for comedication, assessment of long-term ADRs, etc.

Description: The following European research initiatives will be presented:

1. CARING: Cancer Risk and INsulin analoGues
2. SAFEGUARD: Safety Evaluation of Adverse Reactions in Diabetes
3. ISICA: the International Study in Insulin and CAncer
4. Impact of insulin use in the cancer risk of patients with Diabetes Mellitus: a matched case–control study in the Primary Care Centers of Institut Català de la Salut (ICS).

727. Globalisation of Utilisation Research: Current Challenges and Triumphs

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Background: Globalisation of healthcare has brought with it new opportunities in terms of pharmacoepidemiology and drug utilisation research. Cross national comparisons and multi-national studies are becoming increasingly important. Yet globalisation also presents challenges in terms of balancing international and local environments. Diversity in terms of capacity, health systems, available data, financial resources and institutional support are key considerations. Innovative pharmacoepidemioloigcal methods are being developed to overcome some of these challenges combining global knowledge with local capacity and need.

Objectives: The objective of this symposium is to discuss challenges and innovation in pharmacoepidemiology and drug utilisation research in the global context. Researchers, policy makers and health professionals working in drug utilisation or health services research should attend this symposium.

Description: This DUR/HSR SIG endorsed symposium consists of four presentations (1 hour in total) followed by a panel discussion (30 minutes). The four speakers will highlight local challenges facing pharmacoepidemiology and drug utilisation research as well as emerging and innovative methods being used to drive future applications and research. The following topics will be covered.

1. Developing methods to meet local needs in a global environment (Africa)
2. Using pharmacoepidemiologiocal techniques to inform policy and change medicine use (Oceania)
3. Emerging pharmacoepidemiological techniques for exploring multi- national medicines safety issues (Asia)
4. Drug utilisation and health services research to improve public health and health service delivery (Latin America)

A panel discussion led by co-Chairs on the critical issues facing globalisation and the future needs and directions of the global drug utilisation research world will follow the presentations.

728. Introduction to the Canadian Network for Observational Drug Effect Studies (CNODES)

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Background: This symposium will discuss various facets of the CNODES distributed network, including its mission, organization, governance, methodological challenges and opportunities, and early results.

Objectives: The objectives of the symposium are to introduce the CNODES network to an international audience, to share aspects of CNODES' first year of experience with researchers engaged in similar distributed networks around the world, and to form linkages with international colleagues. The symposium is designed to have broad appeal to various researchers including those attendees with a particular interest in drug safety networks.

Description: 1. Introduction: Mission, organization and governance of CNODES

2. Data, ethics, and approaches to assuring quality and minimizing bias

3. Methodological Challenges and Opportunities in CNODES: CNODES uses specialized teams for database analysis and methods. The role of the Methods Team in network studies will be described and an overview of special methodological challenges, including sequential methods for meta-analysis and the assessment of long-term effects of drugs using databases, will be discussed.

4. Results 1: Network Study of High Potency Statins and Acute Kidney Injury: Methods and results of the inaugural CNODES study will be presented. Some of the initial challenges in conducting the first CNODES study will be also discussed.

5. Results 2: Network Study of Proton-pump Inhibitors and Community Acquired Pneumonia: The second CNODES study highlights the potential capacity for database networking to employ extreme cohort restriction to control otherwise intractable confounding.

6. Results 3: Network Study of Atypical Antipsychotics and Diabetic Ketoacidosis.

7. International Perspective: Are there potential synergies between CNODES and other networks?

8. Panel Discussion/Questions and Answers.

729. New Pharmacovigilance Legislation: A Call to Arms to the Pharmacoepidemiology Community

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Background: Although some form of risk management has been in place for a number of years in many pharmaceutical companies, risk management plans (RMPs) only became a formal regulatory requirement in November 2005. The new EU pharmacovigilance legislation, which came into force in July 2012, recognises their importance and places risk management and pharmacoepidemiology at the core of pharmacovigilance in Europe. The implementation of the new legislation brings challenges to and opens opportunities for the pharmacoepidemiology community.

Objectives: To give an update on the main elements addressed by the new pharmacovigilance legislation and to discuss the practical implications for pharmacoepidemiologists of the proposed changes.

Description: A moderator will briefly present key issues of the new PhV legislation (10 minutes). Three presenters will put forward different stakeholders' perspectives on the practical implications of the changes (20 minutes each) The panelists will discuss the issues and questions raised by the audience with the encouragement of the moderator (20 minutes).

Key elements that will be addressed 1. Broad and deep changes to regulation – this is the biggest change in a generation and pharmacoepidemiologists are at its centre.

2. Key priorities of the new legislation are the strengthening of RMPs, post-authorisation safety studies and post-authorisation efficacy studies, and the measurement of effectiveness of risk minimisation measures.

3. A major task will be to assure validity of estimates of both efficacy and safety, so addressing the overall benefit/risk of new medicines in real world usage.

4. Review of opportunities and challenges for different stakeholders.

730. Small Patients, Big Challenges – Current Topics in Pediatric Pharmacoepidemiology

Katia M Verhamme,[1] Sandra de Bie,[1] Timothy Beukelman,[2] Susan A Oliveria,[3] Tamar Lasky,[4] Rachel Sobel.[5] *[1]Medical Informatics, Erasmus University Medical Centre, Rotterdam, Netherlands; [2]Pediatric Rheumatology, Uiversity of Alabama at Birmingham, Birmingham, AL, United States; [3]Episource, New York, NY, United States; [4]MIE Resources, Kingston, RI, United States; [5]Epidemiology, Pfizer, New York, NY, United States.*

Background: Children differ from adults in their metabolism, absorption, and response to medication so that it is

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not always possible to extrapolate results from efficacy and safety studies conducted in adults to the pediatric population. Pediatric patients comprise one of the fastest growing populations being prescribed medications. Pediatric drug development regulations, such as the European Paediatric Investigation Plan (PIP) requirement, have expanded the need for information on drug exposures in pediatric populations. However, studies dedicated to pediatric pharmacoepidemiology present unique methodological and operational challenges.

Objectives: To review the regulatory framework for pediatric drug development and the particular need for, and challenges within, the field of pediatric pharmacoepidemiology, and to demonstrate specific applications and methodologic approaches to meet these challenges. Attendees who would benefit attending this session would include researchers involved in, or those interested in learning more about pharmacoepidemiologic studies of pediatric patients.

Description: The first presentation will describe the rationale for addressing pediatric issues separately from adult issues. The main points will include: background and practice, rationale for changes in regulatory policy, and specific methodological issues. The next presentation will describe approaches for studying pediatric drug safety using multi-country electronic healthcare databases. The third presentation will highlight a unique public-private pediatric disease-based registry developed to study uncommon, latent, and cumulative adverse effects of therapeutics in the treatment of pediatric rheumatic disease. The final presentation will discuss methodological approaches and applications used in pediatric pharmacoepidemiologic studies, including use of administrative databases and electronic medical records. Specific examples from pediatric studies conducted with the HealthCore Integrated Research Database (HIRDSM), Premier Perspective database, and Henry Ford Health System will be presented.

731. The Real Potential of Routine Electronic Health Records for Clinical Trials: Putting Them to the Test

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Background: Reports from major science bodies have highlighted the potential of routine electronic health records for translational health research. A recent article in the British Medical Journal argued that a revolution is long overdue in the technical and research governance frameworks for testing widely used interventions. In various countries, there is an increasing investment in EHR systems (including the UK which will introduce the Clinical Practice Research Datalink).

Objectives: In this symposium, EHR experts and an academic present an overview of the opportunities and challenges of having more EHR records covering larger populations and of using EHR data for randomised clinical trials. Panelists from regulators, industry, and academia will provide different perspectives on this issue.

Description: The symposium will consist of three presentations (45 min total) and a panel discussion (45 min). The presentations will focus on: (1) a description of a major new EHR resource (the Clinical Practice Research Datalink in the UK); (2) the experiences with conducting pragmatic randomised trials and cluster trials within EHR databases; and (3) and a commentary on the scientific opportunities and challenges around the use of EHR data. The panel discussion will include a discussion of the critical issues surrounding the wider application of EHR research, including trials based on EHR data.

732. Rare Serious Adverse Events: Comparison of Patient- and Physician-Reported Outcomes

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Background: The validity of information on clinical outcomes is essential in non-interventional research. In field studies, investigators often have the choice between patient- as well as physician-reported outcomes. In healthy populations – such as users of oral contraceptives – evidence on the accuracy of these methods is scarce. Physicians who recruit healthy subjects into pharmacoepidemiological studies are not necessarily involved in the treatment of serious adverse events (SAEs). Therefore the investigators assumed that physician-reported outcomes under these circumstances might be associated with a lower sensitivity compared to validated patient-reported outcomes.

Objectives: To compare two different methods for detecting rare SAEs: validated patient-reported vs. physician-reported outcomes.

Methods: In the "International Active Surveillance Study of Women Taking Oral Contraceptives", participating women reported SAEs every 6 months. These reports were validated via physicians who treated the reported event (not the recruiting physician). The combination of self-reported outcomes with a rigorous validation process is considered to have high sensitivity and specificity. The incidence rates based on these validated patient-reported outcomes were compared to the rates reported by the gynecologists who recruited the study participants. The two methods were compared by an adjusted McNemar test. For both data collection methods, sensitivities and negative predictive values were calculated.

Results: Overall, 123 gynecologists were questioned about SAEs of 4,572 study participants. These gynecologists

reported only two SAEs (one breast cancer, one thromboembolic event). In contrast 105 validated, serious adverse events were reported by the 4,572 study participants ($p < 0.001$) – including the SAEs reported by the gynecologists. These included seven cancer cases, nine thromboembolic events, 20 diseases of the digestive system, 13 accidents, and 11 infections.

Conclusions: In the study setting, validated patient-reported outcomes have a substantially higher sensitivity compared to physician-reported outcomes. For similar studies it appears sufficient to rely exclusively on validated patient reports.

733. Prevalence and Preventability of Self-Reported Adverse Drug Events – A Cross-Sectional Population-Based Survey in Sweden

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Background: Adverse drug events (ADEs) have been found common and often preventable among hospitalised patients, but no previous study has investigated self-reported ADEs in a representative sample of the general public.

Objectives: To estimate the one-month period prevalence of self-reported ADEs among the adult general public in Sweden, and to estimate the self-reported preventability of two ADE categories: adverse drug reactions (ADRs) and sub-therapeutic effects of drug therapy (STEs).

Methods: In this cross-sectional study, a postal survey was sent to a random sample of 14,000 Swedish residents aged 18 or older in October 2010. The survey was pilot-tested for face and content validity. Self-reported ADEs experienced during the past month included ADRs, STEs, drug dependence, drug intoxications and morbidity due to drug-related untreated indication. ADEs could be associated with prescription, non-prescription or herbal drugs. For ADRs and STEs, the respondents estimated whether the event could have been prevented. The identified self-reported ADEs were analysed descriptively.

Results: Of 7,099 respondents (51.0%), ADEs were reported by 19.4% (95% CI, 18.5–20.3%). The prevalence of self-reported ADRs, STEs, and morbidity due to drug-related untreated indication was equally high, between 7.6 and 8.1% for each. Drug dependence was reported by 2.2% (95% CI, 1.9–2.6%) and drug intoxications by 0.2% (95% CI, 0.1–0.3%) of the respondents. Of 1,377 persons with ADEs, 54.3% reported one, 35.7% 2–3, and 9.9% from four up to 11 ADEs. Of 845 ADRs, 16.6% (95% CI, 14.1–19.1%) were estimated preventable by the respondents, while 22.4% (95% CI, 19.4–25.4%) of 745 STEs were considered preventable. The most common drug classes associated with in total 2,568 ADEs were NSAIDs (7.3%), antidepressants (7.9%), antihypertensives (6.2%), and drugs for insomnia (5.4%).

Conclusions: One fifth of the adult general public reported experiencing ADEs during the past month, indicating that ADEs are a significant disease burden also outside hospitals. As ADRs and STEs were commonly considered preventable, further measures are required in healthcare to prevent ADEs.

734. Medications in Pregnancy Abstracts Presented at ICPE 2001–2009: Trends in Subsequent Publication

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Background: Peer-reviewed publication of abstracts ensures proper vetting and may serve as a measure of the quality of the research.

Objectives: To examine trends in subsequent publication of abstracts focused on medications in pregnancy presented at ICPE from 2001 to 2009 and to examine factors associated with publication.

Methods: We identified 257 applicable abstracts and collected data on affiliation of 1st author, study objective and design. A trained research assistant blinded to the study purpose conducted Medline searches using a standardized algorithm to identify subsequent publications. If a publication was found, the journal and its impact factor were noted.

Results: In 2001, 31% of abstracts were subsequently published, including 50% of oral presentations and 22% of posters. The publication rate increased in 2009 to 57%, including 69% of oral presentations and 53% of posters. Mean journal impact factor increased from 3.8 in 2001 to 5.3 in 2009. In 2001, half of the abstracts were subsequently published in a pharmacoepidemiology or drug safety journal and half in a therapeutically focused journal. In 2009, 46% were subsequently published in a therapeutically focused journal, 33% in a pharma coepidemiology or drug safety journal, and 21% in a national medical journal. Factors associated with subsequent publication in 2001 included 1st author affiliated with pharmaceutical industry and abstract focused on drug impact using a prospective cohort study design. Factors associated with subsequent publication in 2009 included 1st author affiliated with government (75%) followed by academia (60%) and abstract focused on drug impact using a prospective cohort or case–control design.

Conclusions: The increasing publication rate and journal impact factor from 2001 to 2009 suggests the quality of ICPE abstracts on medications in pregnancy may be increasing. Not surprisingly, studies focusing on drug impact using a prospective cohort design were positively associated with subsequent publication in both time peri-

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ods. The shift in 1st author affiliation over the two time periods was unexpected, especially the diminishing representation of publications by pharmaceutical industry authors.

735. Using Electronic Healthcare Records for Drug Safety Signal Detection: A Comparative Evaluation of Statistical Methods

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Background: Drug safety monitoring relies primarily on spontaneous reporting, but electronic healthcare record (EHR) databases offer a possible alternative for detection of adverse drug reactions (ADRs).

Objectives: To evaluate the relative performance of different statistical methods for detecting drug-adverse event associations in EHR data representing potential ADRs.

Methods: Data from seven databases across three countries in Europe comprising over 20 million subjects was used to compute relative risk estimates for drug-event pairs using ten different methods, including those developed for spontaneous reporting systems, cohort methods such as the Longitudinal Gamma Poisson Shrinker (LGPS), and case-based methods like case–control. The newly developed method "Longitudinal Evaluation of Observational Profiles of Adverse events Related to Drugs" (LEOPARD) was used to remove associations likely caused by protopathic bias. Data from the different databases was combined by pooling of data, and by meta-analysis for random effects. A reference standard of known ADRs and negative controls was created to evaluate method performance. Area under the curve (AUC) of the receiver operator characteristic curve was calculated for each method, both with and without LEOPARD filtering.

Results: The highest AUC (0.83) was achieved by the combination of either LGPS or case–control with LEOPARD filtering, but performance between methods differed little. LEOPARD increased overall performance, but flagged several known ADRs as caused by protopathic bias.

Conclusions: Combinations of methods demonstrate good performance in distinguishing known ADRs from negative controls, and we assume that these could also be used to detect new drug safety signals.

736. Drug Safety Signals Detected Using Electronic Health Records and Spontaneous Reporting Systems Data: The Experience of EU-ADR Project

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Background: In the last 10 years, data mining methodologies have been developed using spontaneous reporting system (SRS) databases for drug safety signal detection. Due to limitations associated with SRS, more recently, the pharmacovigilance field has started to explore electronic health records (EHR) for signal detection.

Objectives: To understand retrospectively Signals of Disproportionate Reporting (SDRs) identified for 10 events in the EU-ADR and SRS databases (FDA-AERS and WHO-Vigibase).

Methods: In the EU-ADR Project a set of 10 events warranting priority for monitoring in pharmacovigilance were selected inspected for their association with all possible drugs: Upper Gastrointestinal Bleeding (UGIB), Anaphylactic Shock (AS), Acute Myocardial Infarction (AMI), Rhabdomyolysis (RHABD), Acute Renal Failure (ARF), Bullous Eruption (BE), Neutropenia (NEUTROP), Pancytopenia (PANCYT), Acute Liver Injury (ALI), Cardiac Valve Fibrosis (CVF). For each event, whenever possible, a list of five drugs known to be associated with the event and or not associated with the event was created. In EU-ADR, drugs with statistically significantly ($p < 0.05$) increased RR (≥ 2) were identified as SDRs. In SRS, threshold of EB05 > 2 regardless of case volume was used.

Results: The detection of SDRs in EU-ADR varied based on the nature of the events considered (20% for AMI

80% for UGIB) and increased substantially if the analyses was restricted to the period preceding first regulatory action. Across all 10 events, EU-ADR was able to detect about 53% of known ADR associations and SRS databases approximately 77% of known ADR associations. For associations that were known as non-ADRs, the detection of non-SDRs was very high and at similar extent in both SRS databases. All of the known non-ADR associations were identified as non-SDRs, except for two in EU-ADR, one in FDA-AERS, both concerning ARF.

Conclusions: The detection of SDRs in EHR may change across different types of adverse events and is influenced by the effect of regulatory actions aimed at risk minimization, once the signal is discovered. More analysis is ongoing to understand SDR detection patterns in EHR.

737. Poor Traceability of Biologicals in Adverse Event Reporting Systems

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Background: Biologicals are known for adverse drug reactions (ADRs) that can be batch or product specific, resulting from small differences in the manufacturing process. It is unknown how much of this information is captured in the current adverse event reporting systems.

Objectives: To assess the traceability of biologicals up to the patient level in two major spontaneous reporting systems (SRS): Adverse Event Reporting System (AERS) in the US and Eudravigilance (EV) in the EU.

Methods: The availability of batch numbers for biologicals was studied in a cross sectional study using ADR reports from 2004 to 2010 and compared to small molecule drugs. Vaccines and blood products were excluded. Duplicate reports were merged. Differences in proportions were tested using chi-square statistics.

Results: A total of 2,028,600 unique cases were identified in AERS, reporting a total of 529,527 biologicals (487,359 suspected) and 5,794,644 small molecule drugs (2,221,321 suspected). In EV there were 2,107,737 unique cases, reporting a total of 441,650 biologicals (357,747 suspected) and 5,637,389 small molecule drugs (2,184,080 suspected). Overall batch numbers were available for 24.0% of the suspected biologicals in AERS and 20.8% in EV. For suspected small molecule drugs the proportions were significantly lower; 7.4% in AERS and 4.0% in EV, respectively ($p < 0.001$). In both SRS, consumers were most likely to report a batch number for suspected biologicals (36.3% in AERS, 40.5% in EV), followed by pharmacists (23.2% in AERS, 18.4% in EV), respectively ($p < 0.001$). This pattern differed according to drug class of the biological. The availability of batch numbers for suspected biologicals differed over the years for AERS, but did not show a clear time trend: 2004 (19.1%), 2005 (15.5%), 2006 (30.4%), 2007 (35.8%), 2008 (27.8%), 2009 (21.4%) and 2010 (19.9%). For EV the availability of batch numbers showed a different pattern: 2004 (11.6%), 2005 (11.8%), 2006 (11.9%), 2007 (11.9%), 2008 (22.6%), 2009 (24.1%) and 2010 (22.7%).

Conclusions: The current study shows a need for improving traceability of biologicals, allowing better monitoring of post marketing safety issues.

738. A Matched Cohort Study Examining Digoxin Exposure and Prostate Cancer Mortality

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Background: Digoxin (DIG) exposure has been associated with reduced prostate cancer (PC) incidence in epidemiological studies. Preclinical data suggests that DIG may mediate this anti-cancer effect through inhibition of hypoxia-inducible factor 1-α.

Objectives: This cohort study examines associations between DIG exposure and mortality in men with PC.

Methods: Men diagnosed with PC 2001–2006 were identified from National Cancer Registry Ireland records and linked state-funded pharmacy claims data. Propensity scores for DIG exposure in the 90 days prior to PC diagnosis were estimated. DIG exposed and unexposed men were matched (1:1) within a calliper of 0.2 standard deviations of the propensity score logit, using greedy matching without replacement. Standardized differences were used to assess covariate balance (z-score < 0.1) between matched cohorts. Hazard ratios (HR) for associations between DIG exposure and all-cause (ACM) or PC-specific (PCM) mortality were estimated using Cox proportional hazards models adjusted for age, comorbidity, smoking status, NSAID exposure, tumour stage and grade. Follow-up to 31/12/2009. Categorical exposure-response analyses were carried out using tertiles of exposure (low, intermediate, high) in the 90 days pre-diagnosis.

Results: Five thousand seven hundred and thirty-two PC cases were identified from the linked database. Three hundred and ninety-one cases received DIG in the 90 days pre-diagnosis, of which 387 were matched to unexposed controls. Matched covariate balance was acceptable. Median follow-up 3.3 years. In adjusted analyses, DIG exposure was associated with ACM (HR 1.23, 95% CI 1.02–1.48) and a non-significant increased risk of PCM (HR 1.18, 95% CI 0.67–1.57). Exposure-response analysis showed only the highest tertile of DIG exposure, was not

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significantly associated with PCM (HR 0.94, 95% CI 0.64–1.40).

Conclusions: Despite significant pre-clinical evidence, we did not see a reduction in mortality in men with PC exposed to DIG. Plasma DIG may not reach concentrations to show effects seen *in vitro*.

739. Tamoxifen Therapy and Risk of Dementia in Breast Cancer Patients: A Danish Nationwide Cohort Study

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Background: Growing evidence suggests that women are at decreased risk of dementia compared to men, probably due to a neuro-protective effect of estrogen. Breast cancer patients treated with anti-estrogenic selective estrogen receptor modulators, such as tamoxifen, may be at increased risk of dementia, but the association is not clear.

Objectives: We studied the association between tamoxifen use and dementia in breast cancer patients, and examined a possible time-dependent effect of tamoxifen.

Methods: We used the Danish Breast Cancer Cooperative Group registry to identify all women with incident estrogen receptor positive, stage I or II breast cancer diagnosed between 1990 and 2004, and followed them through 2010. To allow for an induction period, the patients were followed from 1 year after breast cancer diagnosis to identify any type of dementia (Alzheimer's, Parkinsonism, Lewy body dementia, vascular dementia, frontotemporal dementia, multisystem atrophy, progressive supranuclear palsy, corticobasal degeneration, mild cognitive impairment, and atypical Parkinsonism). Information on dementia was ascertained from the National Patient Registry. Cox regression was used to estimate crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: There were 8,446 tamoxifen exposed and 8,359 tamoxifen unexposed breast cancer patients included in the study, and 231 (2.7%) of the tamoxifen exposed and 302 (3.6%) of the tamoxifen unexposed breast cancer patients developed dementia more than 1 year after breast cancer diagnosis. The overall age-adjusted HR of dementia was 1.11 (95% CI: 0.93, 1.33). Between 1 and 4 years after breast cancer diagnosis, the HR for dementia was 1.15 (95% CI: 0.74, 1.79); between 4 and 6 years after breast cancer diagnosis, it was 1.33 (95% CI: 0.83, 2.13). Among dementia subtypes, the overall age-adjusted HR was 1.34 (95% CI: 0.88, 2.03) for Alzheimer's disease, 1.30 (95% CI: 0.77, 2.20) for Parkinsonism, and 1.22 (95% CI: 0.10, 14.4) for atypical Parkinsonism.

Conclusions: In this large prospective study, our results provide no evidence of an association between tamoxifen exposure and rates of dementia in breast cancer patients.

740. Risk of Congestive Heart Failure from Trastuzumab (Herceptin) in Elderly Persons with Breast Cancer: A Population-Based Study

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Background: Randomized trials have reported a 4–5 times increased risk of congestive heart failure (CHF) among breast cancer (BC) patients receiving combined therapy of anthracycline and trastuzumab (T, Herceptin). However, the risk of CHF has not been investigated in general clinical practice, where patients are typically older and have more comorbidities than randomized trial participants.

Objectives: To assess the association between CHF risk and T use in breast cancer patients older than 65 years.

Methods: Using the U.S. SEER-Medicare database, we identified all women newly diagnosed with BC as their primary cancer during 1998–2007, who received chemotherapy with or without T, free of CHF history and followed through 2009. We defined outcomes as the first CHF event after BC diagnosis using diagnostic codes from inpatient and outpatient claims. We calculated propensity score of T use in each patient and apply the inverse-propensity of treatment weighted (IPTW) method in Cox proportional hazard models to estimate CHF risk with T. We modeled receipt of chemotherapy agents as well as cardioprotective agents as time-dependent covariates.

Results: We observed 4,507 CHF events in 69,012 BC patients (median age at diagnosis = 75). Patients aged under 75 years old, in advanced stage, or who had no CVD comorbidity were more likely to receive T. T use was associated with an increased risk of CHF (HR = 2.36, 95% CI = 1.76, 3.16). The increased CHF risk of T use was stronger among patients aged under 75 (HR = 2.46, 95% CI = 1.81, 3.34) than those above 75 (HR = 1.21, 95% CI = 0.77, 1.90).

Conclusions: Compared with clinical trials, this large, population-based cohort study found a lower but still significantly increased CHF risk with T use, suggesting the need for careful selection of patients receiving adjuvant therapy of T among breast cancer patients older than 65 years old.

741. Use of Orlistat and Risk of Colorectal Cancer

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Background: Orlistat is currently the only anti-obesity drug approved for over-the-counter sale in the US and Europe. An animal study showed that exposure to orlistat induced precancerous colonic aberrant crypt foci, but it is unclear whether this would affect risk for colorectal cancer.

Objectives: To examine whether use of orlistat affects the risk of colorectal cancer in adults.

Methods: A retrospective cohort study was conducted using data from the UK General Practice Research Database from September 1998 to December 2008. Eligible patients were adults aged 18 years or older who initiated treatment of orlistat. Each new user of orlistat (n = 33,746) was matched to up to five nonusers (n = 154,747) on age, sex, body mass index (BMI), and start date of treatment. The study outcome was colorectal cancer. Patients were followed until the event occurred or end of study, regardless of treatment discontinuation. We estimated incidence rates per 100,000 person-years for both groups and hazard ratios using Cox proportional hazard models with adjustment of quintile-stratified propensity score.

Results: Of 188,493 patients with a median age of 47 (Interquartile Range, 37–57), 77% were women, and approximately 90% were obese (BMI ≥ 30). New users of orlistat were more likely to have a prior history of diabetes or hypertension and to receive prescriptions of anti-diabetic medication, statins, and aspirin, compared to nonusers. During 645,149 person-years of follow-up, we identified 58 and 304 colorectal cancer cases among new users of orlistat and nonusers, respectively. The colorectal cancer rate was 47.12 for orlistat users and 58.23 for nonusers. After adjustment for propensity score, the hazard ratio of colorectal cancer comparing orlistat initiators to non-users was 0.77 (95% CI: 0.57, 1.03), suggesting that use of orlistat was not associated with a higher risk of colorectal cancer.

Conclusions: This study of UK population shows no evidence of an increased risk for colorectal cancer after the initiation of orlistat.

742. Bisphosphonates and Esophageal Cancer in the GPRD

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Background: In 2009, the US FDA noted reports of esophageal cancer (EsoCA) in persons who had received alendronate or other bisphosphonates. Subsequent epidemiologic studies did not generally find risk elevations. Esophageal reflux is both a risk factor for EsoCA and a relative contraindication to bisphosphonate use, because these products may irritate the esophagus. The present study was designed to address possible artifacts that threatened the previous studies.

Objectives: To estimate the relative incidence of EsoCA in women who used oral bisphosphonates vs. contemporaneously observed women of the same age who did not.

Methods: Two analyses were undertaken in the GPRD, a collection of UK general practitioners' electronic medical records organized for health research. Women born 1922–1953 with records between 1996 and 2008 were followed through 2009. In a case-cohort study, cases of EsoCA identified in the electronic and underlying written practitioners' records were compared to a subcohort of 25,000 women drawn at random with matching on birth year and date of case occurrence, using time-lagged covariates. A second analysis formulated the data as a series of inception cohorts with an intent-to-treat analysis.

Results: Of 684,815 women experienced 929 cases of EsoCA. Users of bisphosphonates were less healthy than randomly chosen age-matched women on a variety of measures. Factors that raised the risk of EsoCA overall were past use of acid suppressant medications, medical indicators of heavy alcohol consumption, both current and past smoking, and very low body mass index. The highest risk for adenocarcinoma was found in women with higher BMI. Under both study designs, use of bisphosphonates more than 2 years before carried a RR of 1.3 (95% CI 1.0–1.7). Alendronate carried RRs of 1.1 and 1.0. There was no evidence of a rising risk with time elapsed since treatment initiation.

Conclusions: These analyses provide no support for the initial concern that alendronate might increase the risk of EsoCA. For all bisphosphonates taken together, the low level of increase, the absence of temporal effects, and demonstrated correlations between bisphosphonate use and other risk factors make a causal interpretation tenuous.

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743. Androgen Deprivation Therapy and the Risk of Colorectal Cancer in Prostate Cancer Patients

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Background: Androgen deprivation therapy (ADT) is a common treatment for prostate cancer, but has become controversial because of its potential cardiovascular adverse effects. Furthermore, it is plausible that this therapy may increase the risk of colorectal cancer, since several *in vitro* studies have suggested a protective role of androgens on colonic carcinogenesis.

Objectives: To determine whether the use of ADT is associated with an increased risk of incident colorectal cancer in patients with prostate cancer.

Methods: All patients with a first-ever diagnosis of prostate cancer, between January 1, 1988 and December 31, 2008, with follow-up until December 31, 2009, were identified within the UK General Practice Research Database. Patients were followed until a first-ever diagnosis of colorectal cancer, death, end of registration with the general practice, or end of the study period, whichever came first. Ever exposure to the different ADTs (gonadotropin-releasing hormone (GnRH) agonists, oral anti-androgens and bilateral orchiectomy) was defined in a time-dependent fashion, allowing patients to move from a period of non-exposure to a period of exposure. All exposures were lagged by one year to account for latency. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using time-dependent Cox proportional hazards models.

Results: The cohort included 21,501 patients with prostate cancer. A total of 184 patients were diagnosed with colorectal cancer during 96,739 person-years of follow-up, yielding an overall rate of 1.9/1,000 persons per year (95% CI: 1.6; 2.2). Ever use of GnRH agonists and oral anti-androgens were not associated with an increased risk of colorectal cancer (HR: 0.83, 95% CI: 0.61, 1.13 and HR: 1.06, 95% CI: 0.64, 1.76, respectively). An over twofold increased risk was observed in patients who underwent bilateral orchiectomy (HR: 2.24, 95% CI: 1.02, 4.94).

Conclusions: The use of GnRH agonists and oral anti-androgens was not associated with an increased risk of colorectal cancer. However, an increased risk was observed with bilateral orchiectomy, which can be due to the permanent nature of androgen suppression with this particular therapy.

744. Optimisation of a Signal Detection Method on Spontaneous Reports of Adverse Events Post Immunisation

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Background: The choice of stratification factors and threshold value for disproportionality signal detection methods may impact the rates of true positive (TP) and false positive (FP) signals detected.

Objectives: To determine the combination of stratification factors and threshold value maximising the number of TP signals while keeping the number of FP signals as low as possible.

Methods: We tested different combinations of stratification factors ((S)ex, (A)ge, (R)egion and (Y)ear) of the Multi-Item Gamma Poisson Shrinker providing 16 different models. For each model 11 different threshold values for the EB05 were tested, from 0 to 2. In total, 176 different models – named by their threshold value followed by the stratification factors (e.g., 2-SARY) – were compared for eight different vaccines. Using the product label of these vaccines as a proxy for true positive safety signals, we compared the performance of each model in terms of Positive Predicted Value (PPV). For each vaccine, models were ranked according to the PPV, with rank = 1 for the model with the highest PPV. Across the eight vaccines, median rank and overall PPV were computed.

Results: The model with the best overall performance across the eight different vaccines was 0.8-SARY, with a median rank of 3 and PPV of 0.2 (195 TP; 763 FP). For a threshold value of 2 the optimal combination of stratification factors differed by vaccine and led to a set of models with a median rank of 34.5 and a PPV of 0.19 (34 TP; 121 FP). Using the SARY set of stratification factors, the optimal threshold differed by vaccine from 0.8 to 2 and led to a set of models with a median rank of 1.75 and a PPV of 0.2 (142 TP; 567 FP). The optimal combination of stratification factors and thresholds provided a different model for each vaccine with a median rank of 1 and a PPV of 0.19 (139 TP; 595 FP).

Conclusions: Stratification and threshold choices substantially impact the detection rate of TP and FP. Within the scope of this exercise, the 0.8-SARY model was considered as the best choice given its high median PPV rank, its high number of TP signals, and the simplicity and robustness of having a unique model for the different vaccines.

745. A Novel Bayesian Hierarchical Model Using Two-Dimensional Groupings of Drugs and Adverse Events for Detection of Adverse Drug Reactions in Large Databases

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Background: The problem of multiple comparisons is of particular concern in pharmacovigilance. Traditional penalisations such as Bonferroni, while conservative, can only treat each drug as independent of other drugs, and each adverse event (AE) as independent of other AEs. This is obviously not the whole story, biologically or chemically. Drugs and AEs can each be related to other drugs and AEs respectively. If a drug increases the incidence of a given AE, we might expect an increase in the same (or similar) AEs for similar drugs. A sensible approach would be to group drugs or AEs according to characteristics that they share, and use Bayesian methods to share information within (and between) those groups. Berry Berry (2004) proposed such a model for AEs, and this has been applied in several studies. However, in each study either the drugs or the AEs were used to build the hierarchy, but never both simultaneously.

Objectives: To develop a Bayesian Hierarchical Model (BHM) with a two-dimensional grouping, incorporating drugs and AEs simultaneously, and to show that this model might produce more powerful results than the one-dimensional BHMs that have been considered in the past.

Methods: We develop a theoretical formulation of our model, and test it on simulated data to demonstrate the concept, and to show that it is behaving as we expect. We also compare our model against a standard frequentist analysis. We then apply our model to real data: a subset of WHO's VigiBase.

Results: For the simulated data, the model behaved as expected. The two-dimensional BHM showed stronger shrinkage, and different AEs are detected when compared to the one-dimensional BHM and the standard analysis.

Conclusions: We find that sharing information in two dimensions does seem to be more effective than sharing only in one. In fact, we find some evidence to suggest that sharing information in one dimension when two are available may actually give misleading results. This is a novel approach, with potentially important benefits for spontaneous reporting databases, such as the WHO's Vigibase.

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746. Temporal Pattern Discovery on Electronic Health Records – A Source of Reference in Signal Detection Work

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Background: In the systematic screening of large collections of individual case safety reports (ICSRs), signals of disproportionate reporting (SDR) are commonly used to select problems for further evaluation. Access to electronic health records (EHRs) could be an important source of reference to support or demote the SDR.

Objectives: To what extent are SDRs in the WHO Global ICSR database, VigiBase, supported/not supported by EHRs from primary care?

Methods: SDRs of drug and adverse drug reaction (ADR) combinations highlighted in the routine signal detection process in VigiBase in the third quarter of 2011 were reviewed. A previously published temporal pattern discovery method was applied on The Health Improvement Network (THIN) data and used as a reference. It displays observed-to-expected ratios for a medical event before and after first prescription of a drug in different time periods (chronograph). Drugs in THIN with at least 100 first prescriptions were included. Combination products and neonatal related ADRs were excluded. Chronographs were reviewed and classified as an increase or decrease after prescription, as a similar pattern before and after prescription, or as inconclusive, i.e., too few events within 12 months after prescription.

Results: Of 568 highlighted drug and ADR combinations in VigiBase, 173 fulfilled the inclusion criteria of which 113 were not labeled and thus analysed in more detail. For 45 combinations, no events were recorded within 12 months after prescription. Thirty-three combinations included numbers sufficient to determine a pattern in the chronograph. One combination had an increase of events after prescription, whilst for nine combinations a decrease was noted (most commonly related to drug indication). Twenty-three had a similar pattern before and after prescription. For 35 combinations, the chronograph was inconclusive, of which six combinations included individual case histories possibly supportive of the highlighted SDR.

Conclusions: Temporal pattern discovery showed to be useful when deciding what SDRs to down prioritize. As individual cases in the EHRs showed to be valuable, a method to systematically highlight significant patient histories is needed.

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747. Uncovering Hidden Patterns in Pharmacovigilance through Robust Subgroup Surveillance

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Background: First-pass screening of individual case safety reports relies on global measures of disproportionality. The underlying data is fundamentally heterogeneous with variability over time, across regions, and types of reports, as well as with the age and gender of patients. Global analyses, adjusted or not, may miss important patterns that exist only in specific data subsets.

Objectives: Implement and evaluate a framework to detect associations between drugs and suspected adverse drug reactions in subsets of individual case safety reports.

Methods: An extract of 5.3 million reports up to February 2010 was taken from the WHO Global Individual Case Safety Reports Database, VigiBase. In addition to global disproportionality analysis, parallel stratified analyses were performed for one or two variables at a time. The covariates included patient age, gender, country of origin, calendar time, country time together, report type, and reporter qualification. For each covariate, measures of disproportionality were computed for all possible subgroups, all-but-one-subgroups, and stratified-then-pooled adjusted measures. Statistics of Disproportionate Reporting (SDR) were defined as those associations for which the lower credibility interval limit of a shrunk odds ratio exceeded 1. Covariate permutation was used to estimate the rates of spurious association due to multiple comparisons, and to set the appropriate width of credibility intervals for each of the stratified analyses.

Results: In addition to 119,500 global SDRs, the subgroup analyses uncovered 14,600 local SDRs at an estimated rate of 2.2% spurious. Examples of uncovered associations include insomnia with salbutamol in children, and hypokalaemia with acetylsalicylic acid in Canada and the US. Covariate permutation analysis indicated that subgroup analyses without correction for multiple comparisons would yield more than 50% spurious among the additionally highlighted SDRs.

Conclusions: Broad subgroup surveillance is computationally feasible and can bring real value by highlighting otherwise hidden reporting patterns. Effective protection against spurious associations is possible and crucial since chance findings are a major concern.

748. A Systematic Analysis of Drug Name Confusion in the FDA AERS Database Using Disproportionality Analysis

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Background: When a spontaneous adverse event report is submitted for potential or actual name confusion of two different medicinal products, this will usually contain the names of both products. In the quantitative analysis of large databases of spontaneous adverse reaction reports such frequent combinations of the same two products will appear as drug interactions.

Objectives: To determine whether the application of quantitative methods to detect drug interactions in databases of spontaneous adverse reaction reports can contribute to the identification of previously unknown name confusion between medicinal products.

Methods: The FDA SRS and AERS spontaneous adverse reaction databases covering 1968 to the 3rd quarter of 2011 were analyzed using the MGPS methodology developed by DuMouchel and the Interaction Signal Score developed by Almenoff, Yang and DuMouchel to identify interactions between drugs for medication errors. This method identifies pairs of drugs occurring together more often than expected on the basis of their individual occurrence. Associations were verified using the List of Confused Drug Names published by the ISMP (June 2011) and FDA Public Health Advisories to identify whether the association was previously known.

Results: Of the 126 drug–drug pairs with an interaction score larger than 1.0, 76 were eliminated as representing either multiple names associated with the same drug, combinations commonly used in polytherapy or genuine drug interactions. Of the remaining 50 drug-drug pairs, 32 were found in the ISMP List or the FDA Public Health Advisories, and were thus considered previously known. The remaining 18 pairs or 14.3% of the drug-drug pairs found, corresponding to a total of 263 case reports, represent cases of drug name confusion which have not been published previously by either the ISMP or the FDA.

Conclusions: The application of quantitative methods to spontaneous adverse reaction databases can provide a valuable contribution to the identification of previously unknown occurrences of product name confusion between medicinal products, and should therefore be incorporated into the standard signal detection best practices within the industry.

749. Utilisation of Fentanyl Buccal Tablets in Primary Care in England: Focus on "Off Label" Use in Support of Risk Management

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Background: Fentanyl citrate buccal tablets (Effentora®; Cephalon) are indicated for the treatment of Breakthrough Pain (BTP) in cancer, in adults who are receiving maintenance opioid therapy for chronic cancer pain. This

study was conducted as part of the risk management plan of the product.

Objectives: To describe the utilisation characteristics of patients prescribed fentanyl buccal, from final results of a Modified Prescription-Event Monitoring cohort, and to assess how the product is being used in relation to terms of license of marketing approval as defined in the Summary of Product Characteristics at time of study.

Methods: An observational cohort post-marketing surveillance study. Exposure data collected from dispensed prescriptions issued by general practitioners (GPs) March 2009–April 2011. Outcome data (indication, event, patient demographic and selected clinical characteristics) from questionnaires sent to GPs ≥6 months after the drug was 1st prescribed for a patient. Summary descriptive statistics calculated.

Results: Final cohort = 551 patients; 54.8% (n = 302) female. Median cohort age = 63 years (IQR: 50–72 years). One reported use in a 14 years old patient. Where specified, primary indications other than BTP reported for 27.9% (133/476) patients including "multiple sclerosis" (n = 7). Regular opioid therapy reported upon starting treatment for 383 patients (69.5% of cohort), though fentanyl buccal is contraindicated in patients who are opioid naive/without maintenance therapy. Sixty-nine patients (12.5%) had ≥1 contraindications for use, including 35 patients with COPD (6.4%). Where specified (n = 433) the most frequent initial titration dose was 100 μg (n = 247) which is in line with prescribing recommendations.

Conclusions: This study has highlighted that some clinicians are prescribing this product outside the recommended terms of the licence, though the majority appear to be adhering to the prescribing recommendations. Drug utilisation studies are important in describing populations that may not have been adequately studied in terms of risk in pre-marketing development programmes and these are important in the post-marketing risk management of medicines.

750. Efficacy of a Structured Prescription Form To Minimize Medication Errors in an Ecuadorian Rural Hospital

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Background: Medication errors are poorly understood and studied in developing world. It is important to develop tools to be used in clinical practice to minimize this risk. The Structured Prescription Forms (SPF) has shown to be effective in in-patients settings but there are no data in out-patients locations. The SPF is a paper tool where the doctor can find all the drugs available at the pharmacy; this way he only has to hand-write the number of units required.

Objectives: To determine the efficacy of a Structured Prescription Form vs. the Traditional Open Form (OPF) to minimize medication errors and improve rational drug use.

Methods: We conducted a pilot before-after trial in the out-patient clinic of a rural hospital in Ecuador. We planned three study phases. During the first phase, all the prescriptions (OPF) dispensed in the hospital pharmacy were collected for 10 days. In the next 5 days, we communicated to medical staff about the trial and how to fill in the SPF. In the last phase, we collected all the forms again. We defined medication error as any missing information about the potency and pharmaceutical form of the prescribed drug, name and signature of the medical doctor and legibility. We were also able to measure indicators of rational use: drugs prescribed in INN.

Results: There were selected 148 OPF and 96 SPFs. In the 1st phase, we identified 63 errors (42.5%) vs. 7 (7.2%) in the 2nd phase. The difference (35.2% [IC95% = 24.9–45.6%]) was statistically significant ($p > 0.01$). The most frequent error found in the OPFs was the lack of information about the pharmaceutical form (18.9% vs. 2.0%), the difference was significant (16.8% [IC95% = 9.1–24.6%]). The number of drugs prescribed according to the INN was higher with the utilization of the SPF (86.5% vs. 69.6%).

Conclusions: The SPFs are effective tools to reduce the medication errors related with the prescription process in out-patients settings. It is particularly important in health services where the electronic prescription is not yet available. The SPFs are also essential to improve rational use indicators. More studies are needed to confirm our preliminary results.

751. Development of a New Type of Risk Minimization Tool To Reduce Medication Errors

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Background: Educational materials, one of the most common types of pharmaceutical risk minimization interventions used, are not highly effective. Written materials are static, non-interactive, and frequently poorly designed. Research suggests that interactive modalities, such as offered by interactive digital technology, may be more effective.

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Objectives: To develop a new risk minimization tool that promotes knowledge and skills acquisition through interactive teaching using digital animation.

Methods: The animation tool was designed to teach parents and caregivers of children with juvenile idiopathic arthritis (JIA) how to assemble and inject a biologic medication. Animation development involved four stages. Stage 1 involved a risk assessment of the vial and syringe assembly process to determine which steps posed potential moderate-high risks. In Stage 2, feedback was elicited from parents regarding the key questions they had about JIA, the drug and drug regimen, and the drug administration process. Stage 3 involved developing an animation prototype that included content tailored to parents stated needs, interactive games to test skills and knowledge acquisition. Stage 4 involved user testing in parents of children with chronic illnesses to determine acceptability, functionality and navigability of the animation. Univariate statistics were used to assess results of user testing.

Results: Results showed that the core content of the tutorial addressed parents' information needs. One hundred percent of participants rated the "Watching the Demonstration" eight-step video and the four interactive tutorials as "most helpful." Participants indicated that they would refer to the animation when they needed a reminder and also use it to train extended family members who might need to help with injections. All respondents, regardless of age or computer literacy, preferred the computer-based, interactive approach over the traditional "instruction booklet."

Conclusions: An interactive, educational animation, such as described here, is highly feasible and acceptable to users and, as such, represents a promising type of "next generation" risk minimization tool.

752. Assessing Physician Compliance To Recommended Liver Function Test (LFT) Monitoring Guidance in Patients with Metastatic Breast Cancer (MBC) Using Lapatinib

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Background: Lapatinib is a dual TKI inhibitor indicated for patients w/HER2-positive MBC. In 2008, the US prescribing information was updated to include a boxed warning w/specific instructions to providers to monitor LFTs. For patient safety, it is important to know the extent to which providers adhere to these guidelines.

Objectives: We aimed to quantify physician compliance w/the boxed warning, which specifically states to conduct a LFT prior to prescribing lapatinib; every 4–6 weeks during treatment; and to discontinue therapy and not retreat if changes in liver function are severe (analysis-defined ALT > 8xULN or Hy's Law). We evaluated compliance before and after the label change to gauge its impact on physician behavior.

Methods: This was a retrospective cohort study using the US Oncology EMR database, comprising a network of over 1,300 community oncology practices and cancer centers in 39 states. Women with MBC who initiated lapatinib March–December 2007 comprised a pre-label change group; those who initiated lapatinib between Jul 9 (official label change date) – December 2008 comprised a post-label change group. Outcomes were proportions w/a LFT within 30 days before drug initiation and within each 6-week treatment period, and the proportion w/a severe elevation that discontinued therapy without restarting. Proportions pre- and post-label change period were tested by Chi-square.

Results: Three hundred and ninety-six female MBC patients, median age 56 years, were included: 128 (32%) in the pre- and 268 (68%) in the post-label change group. Post-label change patients were more likely than pre-label change patients to be tested ≤30 days before initiating lapatinib (82% vs. 63% respectively, $p < 0.0001$) and to be tested w/in each 6-week treatment interval (for example, 81% vs. 68% for 1st 6 weeks, $p = 0.004$ and 83% vs. 62% at 18–24 weeks, $p = 0.01$). Four patients experienced a severe LFT elevation; two pre-label patients who resumed treatment and two post-label change patients with complete discontinuation.

Conclusions: This study provides real-world evidence that physician compliance to LFT monitoring during lapatinib therapy improved after the addition of detailed guidance.

753. Evaluation of Warnings in Labeling: Association of Label Changes and REMS on Physician Discontinuation of Exenatide BID Following Pancreatitis Diagnosis

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Background: Exenatide administered twice daily (ExBID) is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Based on postmarketing AERS spontaneous reports, ExBID was associated with pancreatitis. To mitigate potential risks of pancreatitis, warning labels were added in 2007 and 2009; REMS was issued in 2009 to assess the effectiveness of label changes and disseminate DHCP letters.

Objectives: To assess changes in physician discontinuation of ExBID in patients diagnosed with pancreatitis before and after label changes and dissemination of DHCP letters.

Methods: A search for all healthcare professional (HCP) spontaneously-reported pancreatitis events from 26 May

2005 to 31 October 2010 was conducted using the company's postmarketing safety database for ExBID. Dates of pancreatitis diagnosis and ExBID discontinuation were used to calculate discontinuation rate and average time from diagnosis to discontinuation before and after label changes. Data were stratified by subtype of pancreatitis and level of diagnosis certainty (definite/probable/possible/indeterminate).

Results: Dates of ExBID discontinuation were available for 531 events of HCP reported pancreatitis. The ExBID discontinuation rate prior to any label change was 79% (136/172), compared with 97% (296/304) and 98% (54/55) after subsequent label changes. Among events with known discontinuation status, discontinuation rate was 100% for haemorrhagic and necrotising pancreatitis. Discontinuation rate did not differ significantly (86–91%) by diagnostic certainty. Data on time-to-ExBID discontinuation were available for 461 events. Treatment was stopped within 1 day of pancreatitis diagnosis in approximately 80% of events. The average time from diagnosis of pancreatitis to discontinuation of ExBID was 8 days before label changes, and 4 and 3 days after label changes.

Conclusions: The ExBID label changes, DHCP letters, and REMS were associated with faster discontinuation of ExBID after pancreatitis diagnosis. Following these results, the ExBID REMS requirement was removed by the FDA.

754. Rational Use of Diagnostic Imaging for Acute Low Back Pain in Australia

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Background: Low back pain (LBP) represents a significant health and economic burden. One in four adults experiences LBP in any 12 months period. X-ray and computerised tomography (CT) scans are commonly ordered by health practitioners. The imaging tests make no difference to health outcomes for most patients with LBP and expose them to the potential harms of radiation exposure.

Objectives: To assess the impact of a national program to promote the rational use of imaging in the management of LBP

Methods: Cross-sectional post-intervention survey with random sampling of GPs who did and did not participate in the NPS program. *Setting*: Primary care. *Interventions*: NPS facilitators and radiologists conducted 140 interactive workshops. Key messages included: assess if further investigations are warranted based on a thorough history and physical examination; familiarise with indicators of potentially serious underlying conditions in LBP; and discuss with LBP patients about the limitations of imaging tests. *Outcome measures*: The difference between general practitioners (GP) who participated in the program and those who did not, in terms of knowledge and self-reported imaging test ordering for LBP. *Statistical analysis*: Two-sample test of proportions was conducted to compare the intervention group, with control group 1 which included non-participating GPs from a network where the NPS program was run; and with control group 2 which included non-participating GPs from a network not participating in the NPS program.

Results: GPs who participated in the workshop were less likely to routinely order CTs for LBP than their peers who didn't attend the workshop and were not in the same network. There was a significant difference ($p < 0.01$) between GPs in the intervention group and GPs in control group 2, (48% compared to 34%), did not routinely order CT scans for LBP. While there was also a difference between the intervention group and control group 1 (39%), this was a not statistically significant. No significant difference was noted across the three groups in relation to referring for X-rays.

Conclusions: Educational program in primary care can have an impact on rational use of CT scans for acute low back pain.

755. Determinants of Impact of Drug Safety Warnings: A Retrospective Analysis of Direct Healthcare Professional Communications

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Background: Throughout a drugs' postmarketing lifecycle serious safety issues may emerge that lead to hospitalization, disability or even death. The industry sends, in collaboration with regulators, Direct Healthcare Professional Communications (DHPCs) to inform healthcare professionals of such risks. Following DHPCs drug use has been shown to decrease to a considerable extent for some but not all drugs.

Objectives: To analyze which drug and DHPC related characteristics determine the impact of DHPCs on drug use.

Methods: DHPCs issued in the Netherlands (2001–2007) and monthly dispensing data (2000–2008) were obtained. We performed a multiple linear regression analysis to examine the impact of characteristics related to the drug, including time (from approval) to DHPC, trend in use before DHPC, degree of innovation, type of initial prescriber requested, and characteristics related to the DHPC, including first/repeated DHPC, timing of DHPC

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in the study period, and type of serious safety issue. The outcome variable was defined as the relative change in new drug use (change in use/median use 12 months pre DHPC) post DHPC as determined in interrupted time series ARIMA models for each drug and DHPC pair.

Results: We identified 58 DHPCs for 46 drugs, of which 20 (34.5%) DHPCs resulted in a mean long-term decrease in drug use of 26.7% (95% CI: -15% to -38%). DHPCs sent for drugs that should initially be prescribed by a medical specialist had less impact than drugs initiated by GPs ($p < 0.001$). The impact of DHPCs increased during the study period ($p < 0.05$). Seriousness of the safety issue was relevant, both risk of death and of disability led to significantly lower drug use than hospitalization (both $p < 0.05$). Repeated DHPCs were marginally more effective than first DHPCs ($p = 0.053$). The remaining characteristics had no significant impact (adjusted $R^2 = 0.363$).

Conclusions: Non-specialist drugs, the type of safety issue, DHPCs issued later in the study period and repeated DHPCs increase the impact of DHPCs on new drug use. These results should be considered when additional measures are necessary to improve impact of DHPCs to prevent future safety issues.

756. Statistical Methods for Comparing the Effectiveness of Treatment Regimens in Long-Term Observational Comparative Effectiveness Research (CER) Studies with Time-Varying Treatments

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Background: Comparing the effectiveness of treatments in long-term observational cohort studies (OCS) wherein patients (pts) therapies may vary over time is challenging. In oncology practice "whether", "when", and for "how long" to treat is a dynamic process involving potential time-dependent confounding (TDC) factors. Marginal structural models (MSMs) can account for TDC however MSMs can be inefficient. We propose relatively efficient Cox models, based on time-dependent covariates, which incorporate pts dynamic treatment patterns.

Objectives: To develop modeling approaches which are capable of incorporating dynamic treatment patterns seen in comparative effectiveness research (CER) studies under conditions when TDC is present.

Methods: To capture pts treatment histories over follow-up in a Cox model, we consider (cumulative) treatment duration and intensity (treatment duration/time) measures as time-dependent covariates. To facilitate clinical interpretation we develop K-M estimators for survival distributions corresponding to treatment patterns ("always treated", "never treated"). The methods are applied to the ARIES OCS to evaluate Bevacizumab maintenance therapy in treating lung cancer. The methods are compared in a simulation experiment designed to mimic a study with time-varying treatments in the presence of TDC.

Results: The performance depends on the degree of TDC. Correctly specified Cox (PH) models are unbiased in the absence of TDC. In our simulations the degree of TDC corresponds to the departure from the PH assumption. The (cumulative) duration model is fairly robust for estimating hazard ratios (relative bias $\leq 10\%$) under a wide range of TDC and sample sizes ($n \geq 300$). Treatment patterns ("always" vs. "never") are also well estimated (under alternative and null). In addition, the duration model can have substantial efficiency gains over MSMs.

Conclusions: In our simulations the (cumulative) duration and intensity Cox models perform well in estimating hazard ratios and treatment patterns under realistic TDC conditions. We suggest that the methods can complement MSMs in the CER setting.

757. A Comparison of Methods for Estimating Exposure-Time Trends in Case-Case-Time-Control Designs

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Background: Case only study designs, such as the case-crossover (CC), use within-person comparisons to control time-invariant confounding. Additional adjustment measures are required to handle time varying confounders such as exposure-time trends. The case-case time-control (CCTC) approach uses estimates of time-trends in reference drugs among cases to adjust for exposure-time trends in CC estimates.

Objectives: To explore the impact of different methods of estimating exposure-time trends in a CCTC study.

Methods: We empirically investigated the impact of control selection in a CCTC study of the short-term risk of death related to use of preventive medications (statins, oral hypoglycemics, antihypertensives, osteoporosis drugs, and glaucoma medications) – a relation known to be biased by time-varying confounding – among Medicare beneficiaries in two US states. Each class was evaluated separately with the remaining four used as reference drugs. We compared analyses which adjusted for exposure-time trends estimated among cases with crossover in the exposure of interest (i.e., cases that contributed to the case-crossover estimate) to analyses which estimated exposure-time trends among all cases meeting eligibility criteria.

Results: CC point estimates (unadjusted for exposure-time trends) indicated that the odds ratio (OR) for death when exposed relative to when unexposed to five different classes of preventive medications were between 0.38 and 0.50, reflecting large time-varying confounding. When exposure-time trends were estimated only among those who contributed to the case-crossover, the analysis

resulted in over-adjustment, with ORs between 1.40 and 1.68. Adjusting for exposure-time trends among all cases resulted in estimates consistent with expectation (ORs ranged between 0.90 and 1.29)

Conclusions: Estimating exposure time trends among only cases who contribute to case-crossover estimates can introduce selection bias. If estimating exposure-time trends among cases, all cases meeting eligibility criteria should be used. Choice of reference drugs for exposure-time trend estimation must be carefully considered.

758. Utility of the Nested Case Control Design for Risk Assessment in the Presence of an Important Risk Modifier in Pharmacoepidemiological Studies: Evidence from Simulated Data

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Background: The nested case control design (NCC) offers a simple alternative when evaluating a time-dependent treatment effect. Its strength rests largely on the appropriateness, within a specific cohort, of the controls matched to the cases and studies suggest a matching strategy that ensures maximizing the number of discordant case–control pairs (counter-matching on the treatment variable) may be more efficient. However, not much is known about the situation where treatment effect may be modified by a known risk factor. Inadequate handling of such a factor can lead to bias in risk estimates, particularly in situations of rare occurrence.

Objectives: To assess the extent of bias associated with effect estimation between three methods of handling an effect modifier in the NCC design compared to results from a cohort study based on simulated data.

Methods: In each simulation, we assumed an underlying hazard of Weibull distribution with inputted values for the scale and shape parameters, treatment (*T*), three risk factors and an effect modifier (R). One hundred sets of cohorts of 1,000 subjects were generated. We applied the classical NCC as design I, counter-matching on T only as design II and on both T and R as design III. Effect modification (EM) was measured as the ratio of hazard ratio (T = 1 vs. T = 0) when risk factors are present (R = 1) vs. absent (R = 0). We defined "bias" as the absolute difference in EM measures between the cohort and each design.

Results: Designs I and II gave EM estimates which in most runs were more than twice those of the cohort-corresponding mean bias of 7.1 (9.1) and 6.4 (13.7) compared with 1.9 (2.0) for III. Indeed, designs I and II crashed in about 5% and 13% of runs, respectively, due to empty strata cells.

Conclusions: Counter-matching on both treatment and effect modifiers in an NCC gave less biased estimates for treatment when such factors are present. This benefit may be particularly important for studies involving rare events.

759. Calendar Time as an Instrumental Variable in Nonexperimental Comparative Effectiveness Research of Dynamic Therapies

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Background: The presence of unmeasured confounding limits the ability of covariate adjustment to reduce bias in pharmacoepidemiologic studies. Instrumental variables (IV) replace the assumption of no unmeasured confounding in adjusted analyses with the notion that the IV affects the outcome only through treatment. For new-to-market therapies that have experienced dramatic changes in clinical practice, calendar time is a potentially strong IV. In Comparative Effectiveness Research (CER) using claims data, IVs. may outperform adjustment in reducing bias because they do not require covariate-rich data.

Objectives: Evaluate the use of calendar time as an IV compared to propensity scores (PSs) in estimation of the hazard ratio (HR) for all-cause mortality among colon cancer (CC) patients.

Methods: Stage III CC patients aged 65+ initiating chemotherapy between 2003 and 2006 were examined using population-based cancer registry data linked with Medicare claims. Cox models were used to estimate HRs. A calendar time IV was constructed to delineate patients treated prior to oxaliplatin FDA approval (pre-November 2004, n = 2013) from those treated after (n = 1175). We examined IV strength and compared estimates with HRs adjusted with a calendar time-specific PS, which allows the propensity for treatment receipt to change over time.

Results: Overall, 863 patients received oxaliplatin and 2,325 received 5-FU only. Calendar time was a robust IV, as it was strongly related to treatment (13.7% vs. 50.0% exposed to oxaliplatin pre- and post-approval) and unassociated with measured confounders. The IV HR (95% confidence interval) for mortality was 0.44 (0.29, 0.68) compared to 0.72 (0.56, 0.93) with PS adjustment.

Conclusions: In this CER analysis, IVs. and PS adjustment both indicate a survival advantage in patients treated with oxaliplatin, albeit with markedly different point estimates. The IV appears to exaggerate the magnitude of oxaliplatin effectiveness while being less precise. This result may be affected by stage migration or changes in survival

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over time beyond treatment. As these HRs are based on very different assumptions, the IV analysis strengthens the evidence of effectiveness.

760. Cox's Proportional Hazards Regression Using Instrumental Variables

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Background: The estimation of treatment and exposure effects is one of the primary goals of statistics in medicine. Estimation based on observational studies is subject to confounding. Statistical methods for controlling bias due to confounding include regression adjustment, propensity scores and the emerging method of inverse probability weighted estimators. None of these methods can remove bias due to confounding, unless all confounders are recorded in the data. The method of instrumental variables can reduce or eliminate bias in observational studies even in the absence of information on confounders. Despite rising popularity this method has not yet been adapted to time-to-event analysis.

Objectives: To derive a method for employing instrumental variables within the framework of Cox's proportional hazards model.

Methods: We define an instrument as a variable correlated with the exposure or treatment but uncorrelated with the martingale residual. Based on this definition, we derive an estimating equation that is very similar to the score equation of the partial likelihood.

Results: We demonstrate the method using an observational study that evaluated the effect of coronary catheterization on survival. Small sample properties of the estimator are addressed in simulations.

Conclusions: This method of hazard ratio estimation using instrumental variables demonstrates excellent properties in comparison to Cox model hazard ratio estimation if there is residual confounding.

761. Primary Non-Compliance and Its Determinants: Implications for Misclassification of Drug Exposure

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Background: Computerized prescribing has provided unprecedented opportunities to evaluate primary non-compliance – the failure to fill the initial prescription – as electronic prescription information is linked with dispensing data from pharmacy systems. Primary non-compliance is a contributor to suboptimal disease management, and a source of bias in drug exposure classification in pharmacoepidemiological studies.

Objectives: To estimate the incidence of primary non-compliance in primary care practice, and the drug (therapeutic class, drug cost), patient (age, sex, co-morbidity, health service use) and physician (practice experience, sex) characteristics that are associated with a greater risk of non-compliance.

Methods: All incident prescriptions written for 15,961 patients in a primary care network of 80 physicians in Quebec, Canada using electronic health records were retrieved between 2008 and 2009. Dispensing data from community pharmacies is integrated and displayed in the electronic health record system; data provided through the provincial insurance provider. Primary non-compliance was defined as failing to fill an incident prescription within 9 months. Multivariate alternating logistic regression was used to estimate predictors of non-compliance and account for patient and physician clustering.

Results: Overall, 31.3% of the 37,501 prescriptions were not filled. Drugs in the upper quartile of cost were least likely to be filled (OR: 1.18; 95% CI: 1.09, 1.23), as were skin agents, hormones, gastro-intestinal drugs, and psychotropic drugs compared to anti-infectives. Increasing patient age was associated with a reduction in the risk of non-compliance (OR: 0.73 [per 10 years] 95% CI: 0.70, 0.75) as was the elimination of prescription co-payments for low-income groups (OR: 0.34; 95% CI: 0.30, 0.38). Greater co-morbidity and recent hospitalization increased the risk of non-compliance.

Conclusions: Primary non-compliance is common, particularly for some drugs, and patient subgroups. Predictors of non-compliance could be used to focus follow-up on high-risk groups, and estimate the probability of drug exposure in pharmacoepidemiological studies.

762. Guillain-Barré Syndrome and Adjuvanted Pandemic Influenza A (H1N1) 2009 Vaccine: Multinational Self Controlled Case Series Study in Europe

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Background: Based on *a priori* concerns around the risk of Guillain Barré syndrome (GBS) following the 1976 swine flu vaccination campaign in the USA, active surveillance programs were enhanced during the pandemic influenza A/H1N1 2009 virus (A(H1N1)pdm09) mass immunization campaigns.

Objectives: To estimate the risk of developing GBS following A(H1N1)pdm09 vaccination.

Methods: A self controlled case series (SCCS) was performed in Denmark, Finland, France, Netherlands, Norway, Sweden, and UK. Information was collected according to a common protocol and standardized data collection. Cases levels 1–4a according to the Brighton Collaboration case classification were included in the analysis. The risk window was 42 days after vaccination. We adjusted for calendar month and if possible for gastrointestinal, influenza like, and upper respiratory infections. Conditional Poisson regression was used for estimation of the relative risk. Pooling was done using a random effects approach.

Results: Three hundred and three GBS and its variant Miller Fisher syndrome cases were included in the study. The most frequently A(H1N1)pdm09 vaccines used were adjuvanted (Pandemrix and Focetria). The unadjusted pooled risk ratio (RR) for all countries was 3.51 (95% CI, 2.32–5.32). After adjustment for calendar month, the pooled RR, was 1.95 (95% CI, 1.22–3.13). Applying the pseudolikelihood method while adjusting for calendar month the pooled RR was 1.91 (95% CI, 1.14–3.22). In countries where further adjustment for infections was possible (NL, NO, UK) the RR decreased from 1.95 to 1.33 (95% CI, 0.51–3.48). Based on the upper limit of the confidence interval of the calendar month-adjusted estimate at most three excess cases of GBS per 1 million vaccinated persons could be expected.

Conclusions: This study shows the feasibility of conducting European collaborative vaccine safety studies. Acknowledging that full adjustment was not possible in all countries, it is estimated that the maximum number of excess GBS cases after (A(H1N1)pdm09) vaccination would be 3 per million vaccinated at most.

763. Self-Controlled Analyses of the Risk of Guillain–Barré Syndrome Associated with Influenza A(H1N1) 2009 Monovalent Vaccines

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Background: The 1976 H1N1 influenza vaccine was associated with a significant increased risk of Guillain–Barré syndrome. The Centers for Disease Control and Prevention Emerging Infections Program implemented active, population-based surveillance for Guillain–Barré syndrome (GBS) following 2009 H1N1 vaccines.

Objectives: To evaluate the relative risk and estimate the attributable risk of GBS following 2009 H1N1 vaccination using self-controlled methods, which avoid potential confounding from person-level factors and co-morbidities.

Methods: Among a population of 45 million persons residing in 10 states/metropolitan areas of the United States, surveillance officers identified GBS cases with symptom onset during October 2009–April 2010 and ascertained receipt of 2009 H1N1 vaccines. Medical and vaccination history was determined through medical chart review and patient interviews. We calculated self-controlled relative risks by comparing the number of cases with onset during a risk interval 1–42 days after vaccination with cases with onset during fixed (days 43–84) or variable (days 43–end of study period) control intervals. We calculated attributable risks by applying statistically significant relative risks to an independent estimate of GBS incidence.

Results: Fifty-nine GBS cases received H1N1 vaccine with or without seasonal vaccine. The relative risk was 2.1 (95% CI 1.2, 3.5) by the variable-window and 3.0 (95% CI 1.4, 6.4) by the fixed-window analyses. The corresponding attributable risks per million doses administered were 1.5 (95% CI 0.3, 3.4) and 2.8 (95% CI 0.6, 7.4).

Conclusions: These attributable risks are similar to those of some previous formulations of seasonal influenza vaccine (about one to two cases per million doses administered), suggesting a low risk of GBS following the H1N1 vaccine that is not clearly higher than that of some seasonal influenza vaccines.

764. Estimating Influenza Vaccine Effectiveness Using a Natural Experiment

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Background: Trivalent influenza vaccine has long been recommended for end-stage renal disease (ESRD) patients, however little is known about its effectiveness in preventing clinical health outcomes. Observational studies

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of vaccine effectiveness (VE) can be biased because vaccinated patients may be healthier than unvaccinated patients.

Objectives: To estimate the effectiveness of influenza vaccine in preventing clinical health outcomes among a high-risk population using a novel study design.

Methods: Usig United States Renal Data System data, we estimated VE for influenza-like illness (ILI), influenza/pneumonia hospitalization, and mortality in adult, patients on hemodialysis using a natural experiment created by year-to-year variation in the match of the influenza vaccine to the circulating virus. Matched (1998, 1999, 2001) and mismatched (1997) years among vaccinated patients were compared using Cox proportional hazards models. Ratios of hazard ratios (HRs) compared vaccinated patients between 2 years and unvaccinated patients between 2 years. VE was calculated as 1 – effect measure.

Results: Vaccination rates were < 50% each year. Conventional analysis comparing vaccinated with unvaccinated patients produced average VE estimates of 13%, 16%, and 30% for ILI, influenza/pneumonia hospitalization and mortality respectively. When restricted to the pre-influenza period, results were even stronger, indicating bias. The pooled ratio of HRs comparing matched seasons to a placebo season resulted in a VE of 0% (95% CI: -3,2%) for ILI, 2% (95% CI: -2,5%) for hospitalization, and 0% (95% CI: -3,3%) for death.

Conclusions: Compared to a mismatched year, we found little evidence of increased VE in subsequent, well-matched years. This suggests that the current influenza vaccine strategy may have a smaller effect on morbidity and mortality in the ESRD population than previously thought. Alternate strategies (high dose vaccine, intradermal vaccine, and adjuvanted vaccines) should be investigated to achieve better health outcomes.

765. The Risk of Immune Thrombocytopenic Purpura Associated with Vaccines in Adults: A Multicenter Case–Control Study

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Background: Immune thrombocytopenic purpura (ITP) is thought to result from an autoimmune mechanism. Studies have suggested vaccinations as a trigger through molecular mimicry.

Objectives: This multicenter case–control study investigated relationships between ITP and vaccination in adults. It also focussed on the two most common vaccines in the study population, against influenza and diphtheria-tetanus-pertussis-poliomyelitis (DTPP).

Methods: Between April 2008 and June 2011, 21 internal medicine and hematology referral centers across France recruited newly diagnosed cases of primary ITP, aged 18–79 years and fulfilling American Society of Hematology criteria. Controls were recruited from general practice settings in the same geographically diverse areas as the cases. A maximum of five controls were matched to each case on: age (±2 years), gender, region of residence (northern or southern France), index date (date of first symptoms for cases and date of recruitment consultation for controls, ±2 months) and season of the index date (spring/summer or fall/winter). Vaccinations and other potential risk factors for ITP were assessed in a standardized telephone interview. The interviewer was blind to case/control status. Cases and controls were compared for vaccination in the 6 and 12 months before the index date, using odds ratios (OR) from conditional logistic regression.

Results: Two hundred and twenty-eight eligible cases of ITP were recruited and 207 were included in the analysis. Of 10,541 eligible controls were recruited and 917 were matched to cases. Seventy cases (33.8%) and 324 controls (35.3%) received at least one vaccination within the 12 months before the index date. Cases and controls were similar for the proportions vaccinated in the previous 6 or 12 months (adjusted OR for 12 months 0.96, 95% confidence interval 0.67, 1.37). This conclusion did not change when vaccines against influenza and DTPP were analyzed separately.

Conclusions: This systematic case–control design is well-suited to study rare disorders such as ITP and few such studies have been conducted. We found no evidence of an increase in the risk of ITP following vaccination.

766. Risk of Febrile Convulsions after MMRV Vaccination in Comparison to MMR or MMR + V Vaccination

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Background: In July 2006 a combined measles-mumps-rubella-varicella (MMRV) vaccine was licensed in Germany. Clinical data showed an increased risk of fever in children who received a 1st dose of MMRV compared to children who received a 1st dose of MMR or MMR and V separately on the same day (MMR + V). A meta-analysis of these data, although not conclusive, suggested an increased risk of febrile convulsions (FC).

Objectives: To estimate the risk of FC after 1st dose vaccination with MMRV in comparison to vaccination with MMR or MMR + V in pre-specified time-windows.

Methods: We performed a cohort study based on claims data from four German statutory health insurance providers (SHIs) covering >14 million insurants throughout Germany. All insurants born in the study period (01.01.04–31.12.08) who received a 1st dose vaccination with MMRV, MMR or MMR + V were included in the cohort. Members of the MMRV group were matched individually to members of the MMR and MMR + V groups with respect to sex, age at immunization, calendar month and SHI. Cases of FC were defined as hospitalizations with a diagnosis of FC where no neurological condition was coded as main discharge diagnosis. Additionally to unadjusted risk ratios (RRs), confounder adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to compare the MMRV group with MMR and MMR + V groups using a binary logistic regression model for each risk interval.

Results: In the main risk period 5–12 days after immunization 18 cases of FC were observed among 82,532 MMRV-vaccinated children, 10 cases were observed among 149,129 MMR-vaccinated children and two cases were observed among 39,164 MMR + V-vaccinated children. This results in an unadjusted RR of 1.8 (95% CI 1.4–2.4) for the comparison with MMR, and an unadjusted RR of 1.3 (95% CI 1.0–1.8) for the comparison with MMR + V. The adjusted adjusted ORs are 2.4 (95% CI 1.4–4.0) for the comparison with MMR and 1.3 (95% CI 0.8–2.4) for the comparison with MMR + V.

Conclusions: This study suggests a twofold increase in the cumulative incidence of FC 5–12 days after a 1st dose immunization with MMRV compared to MMR vaccine and a 1.3–1.5-fold increase compared to MMR + V immunization.

767. Surveillance of Pertussis in The Netherlands: Monitoring the Impact of Recent Changes in the Vaccination Program

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Background: Because of a pertussis-upsurge since 1996, an acellular booster was added to the NIP in late 2001. Furthermore, an acellular vaccine replaced the whole cell vaccine at infancy in 2005.

Objectives: To measure the impact of these interventions on the Dutch pertussis-epidemiology.

Methods: Disease-, immuno- and pathogen-surveillance were used for monitoring. The "screening"-method was used to calculate age-specific vaccine-effectiveness.

Results: Overall mean incidence of notifications per 100,000 increased from 32 (1996–2004) to 37 (2005–2010). Mean incidence in 0-year-olds decreased from 123 (1996–2004) to 88 (2005–2010). Likewise, mean incidence in 1–4-year-olds decreased from 123 to 52. In 5–9-year-olds mean incidence decreased from 174 (1996–2001) to 112 (2002–2010). In persons ≥10 years, mean incidence increased from 15 (1996–2004) to 33 (2005–2010). Likewise, immunosurveillance data showed an increase of pertussis-specific antibodies from 4% (1996–1997) to 9% (2006–2007). Mean vaccine-effectiveness in 1–3-year-olds increased from 31% (1996–2004) to 81% (2005–2010). In the cohorts targeted for the booster vaccination vaccine-effectiveness remained high (mean 64%) with still 28% in the first two cohorts vaccinated, i.e., 8–9 years after introduction of vaccination.

Conclusions: Due to changes in the vaccination program, the incidence of pertussis is decreasing in children. Vaccine-effectiveness considerably improved after introduction of an acellular vaccine. More than 5 years after its implementation, vaccinated cohorts still benefit from the introduction of a preschool booster dose. In contrast, the incidence of pertussis in adults is increasing, probably due to increased circulation following pathogen adaptation. Further optimization of the vaccination strategy should be addressed.

768. Effectiveness of the Influenza A(H1N1)pdm09 Vaccine in Adults Recommended for Annual Influenza Vaccination: A Case–Control Study

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Background: Because of variability in published A(H1N1)pdm09 influenza vaccine effectiveness estimates, we aimed to assess the effectiveness of MF59-adjuvanted A(H1N1)pdm09 vaccine in a matched case–control study.

Objectives: We aimed to assess the effectiveness of MF59-adjuvanted A(H1N1)pdm09 influenza vaccine in a matched case–control study.

Methods: This study was conducted during the pandemic influenza season 2009–2010 in adults with underlying comorbidities and healthy subjects of 60 years and older recommended for annual influenza vaccination in the Netherlands. Sixteen laboratory- confirmed and eligible A(H1N1)pdm09 influenza cases registered by four Community Health Services of the Netherlands were included. The control population was retrieved from a general practice database and consisted of subjects who had not been registered with influenza code R80 (according to the International Classification of Primary Care) during the A(H1N1)pdm09 influenza season. The controls were matched to cases on sex, age and comorbidities. The primary outcome was laboratory-confirmed A(H1N1)pdm09 influenza. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated. Vaccine effectiveness (VE) was expressed as VE = (1 - OR)*100%.

Results: The A(H1N1)pdm09 vaccination rates in cases and controls were 6% and 76% respectively. After matching cases with controls in a ratio of 1:10, vaccine effectiveness was 98% (95% CI 84–100%).

Conclusions: Even though we cannot entirely rule out that selection bias has played a role in our study, the present results indicate that the MF59-adjuvanted A(H1N1)pdm09 influenza vaccine has been effective in preventing laboratory-confirmed A(H1N1)pdm09 influenza in adults with underlying comorbidities and healthy subjects of 60 years and older during the A(H1N1)pdm09 influenza pandemic.

769. Abstract withdrawn by author.

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772. The Risk of Juvenile Arthritis Following Quadrivalent HPV Vaccination: The Ontario Grade 8 HPV Vaccine Cohort Study

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Background: There has been a great deal of controversy about the safety of the human papillomavirus (HPV) vaccine. Despite the fact that the incidence of juvenile arthritis is high in age groups targeted for HPV vaccination and the condition has been associated with other vaccines, it has yet to be studied in relation to the HPV vaccine.

Objectives: To evaluate the risk of arthritis following quadrivalent HPV vaccination in Grade 8 girls.

Methods: We identified a population-based cohort of all girls residing in Ontario's Kingston, Frontenac, Lennox, and Addington health region who were eligible for the province's Grade 8 HPV vaccination program during the 2007–2008 and 2008–2009 school years. We used Ontario immunization and health databases to identify dates of HPV vaccination and diagnoses of arthritis. Using the self-controlled case series, we estimated the rate ratio (RR) and 95% confidence interval (CI) of arthritis during the 60 days following a dose of the HPV vaccine, adjusted for age. We also assessed the potential of time-varying risk by dividing the 60-day risk window into smaller, consecutive risk periods.

Results: We identified a cohort of 2,519 girls, 14 of whom were "exposed cases" (i.e., received the HPV vaccine and were diagnosed with arthritis). HPV vaccination was associated with a >fourfold increase in the risk of arthritis in the 60 days following administration of a dose (RR 4.33, 95% CI 1.36–13.73). The risk was inestimable between days 1 and 7 (0 cases), increased twofold between days 8 and 21 (RR 2.03, 95% CI 0.44–9.27), increased fourfold between days 22 and 60 (RR 4.06, 95% CI 1.36–12.1), and returned to baseline between days 61 and 100 (RR 1.00, 95% CI 0.27–3.68).

Conclusions: These results provide preliminary evidence of an increased risk of arthritis following quadrivalent HPV vaccination in girls aged 13–15 years. Given the small sample size, we are currently verifying our findings in a province-wide cohort of approximately 300,000 girls. These results will be available for presentation by August 2012.

773. Temporal Scan Statistics for Vaccine and Drug Safety Studies

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Background: In an application proposed by Margaret Kolczak, temporal scan statistics have proved very useful for vaccine safety studies. They are used to determine if potential adverse events are clustered in some window of days after vaccination, without assumptions about the location or width of the risk window. The method adjusts for the multiple testing arising from the many risk windows evaluated. As an example, the method played a key role in finding that MMRV causes an excess risk of seizures 7–10 days after vaccination. The method is also used for drug safety.

Objectives: In this methodological study, we evaluate the potential bias of the temporal scan statistic due to age, day-of-week effects and loss to follow-up. For the first time, we describe ways to adjust for such bias.

Methods: Using data from the CDC sponsored Vaccine Safety Datalink, we compared unadjusted and adjusted temporal scan statistics for three different vaccine-outcome pairs: MMRV seizures, RotaTeq intussusception, and, influenza vaccine miscarriage. We also made comparisons using artificial simulated data, with known properties.

Results: For seizures, results are the same with and without adjustments. Due to rapidly changing intussusception incidence by age, the temporal scan statistic is biased unless adjusted for age. Due to weekly variation in miscarriage reporting, it is biased unless adjusted for day-of week effect. When the temporal scan statistic is used for time periods more than a few months after vaccination, it is important to adjust for loss to follow-up. The temporal scan statistic can be adjusted for these factors using adjusted expected count or stratified randomization, removing the bias. Simulations provide estimates for the magnitude of the bias. For example, suppose that both vaccines and outcomes are equally distributed among the 5 weekdays, with no vaccines or outcomes on weekends. Without adjustments, and with nominal $\alpha = 0.05$, the null is rejected with probability 0.08 when there are 100 events, 0.24 with 500 events and 0.48 with 1,000 events.

Conclusions: It is sometimes important to adjust the temporal scan statistic for age, day-of-week effects, or premature loss to follow-up. This can be done.

774. Disproportionality Analysis of Vaccine Reports – A Comparison of VAERS and VigiBase

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Background: As part of the World Health Organization Blueprint project, the U.S. Food and Drug Administration transmits Vaccine Adverse Event Reporting System (VAERS) reports to the Uppsala Monitoring Centre (UMC) for inclusion in the Global Individual Case Safety Report database, VigiBase. Although VigiBase includes reports from 105 countries participating in the WHO Programme for International Drug Monitoring, over 50% of reports in the vaccine portion of VigiBase originate from VAERS. Yet, there is no information if and in what respects VAERS and other VigiBase reports diverge.

Objectives: To examine statistics of disproportionate reporting (SDRs) in VAERS and all vaccine reports in VigiBase (VaccVigiBase) that might contribute to discordant results for several products and adverse events of interest.

Methods: The February 15, 2011 version of VigiBase was partitioned into vaccine reports from all countries including VAERS (VaccVigiBase) and vaccine reports from VAERS only (VAERS). SDRs, defined as combinations of products and MedDRA preferred terms (PTs) with a value exceeding 0 at the lower bound of the 95% credibility interval surrounding the Information Complement ($IC025 > 0$), were calculated with stratification by age and country of origin. To examine the differences in SDRs two separate vaccines were selected MMRV (high proportion of VAERS) and Tetanus and Diphteria (TD) vaccines (low proportion of VAERS). A separate analysis of all vaccines examined SDRs with specific vaccine related PTs: febrile seizure and anaphylaxis.

Results: There are differences in ADR terms used, age distribution and vaccine usage. Nearly 25% of SDRs for MMRV and 10% of SDRs for TD were present only in VaccVigiBase. Vaccines with $IC025 > 0$ for febrile seizure in VaccVigiBase alone included meningococcal, typhoid, and a product not distributed in the US. Vaccines with an $IC025 > 0$ for anaphylactic reaction in VaccVigiBase alone included human papillomavirus and two products not distributed in the US.

Conclusions: Despite the substantial influence of VAERS on VaccVigiBase, this study highlighted important differences in the datasets. The method used here holds promise for hypothesis generation on a global scale.

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775. Patterns and Predictors of Rotavirus Vaccine Use among Commercially-Insured U.S: Infants

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Background: In February 2006, a new pentavalent rotavirus vaccine (RV5) was recommended for routine use among U.S. infants, and in June 2008, a monovalent rotavirus vaccine (RV1) was also recommended by the Advisory Committee on Immunization Practices (ACIP). RV5 requires three doses, while RV1 requires just two doses to complete the series.

Objectives: Our study compared individual, provider, and ecologic predictors of rotavirus (RV) vaccine use among commercially insured U.S. infants from 2006 to 2010. We also examined the timeliness of vaccine administration as per the ACIP recommendations, and completion of the vaccine series.

Methods: RV vaccination status and nine potential predictors were obtained from the MarketScan® Research Databases. An additional variable measuring rurality was abstracted from the U.S. Department of Agriculture, Economic Research Service. Cohort eligibility included continuous enrollment, a birthing code prior to October 2010, residence in a state without a universal RV vaccination program, and data on all predictors. We calculated simple frequencies, and performed bivariate analyses and multivariable logistic regression.

Results: Nearly 69% of 423,869 eligible infants received at least one dose of RV vaccine. In multivariable analyses, the strongest predictors of RV vaccination were receipt of the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine (OR = 24.48, 95% CI = 23.63–25.37), and visiting a pediatrician vs. family physician (OR = 3.57, 95% CI = 3.47–3.68). Most infants received the RV vaccines at the recommended ages, but more infants completed the series for RV1 than RV5 or a mix of the two vaccines (87.0% vs. 80.0% vs. 72.9%).

Conclusions: A variety of individual, provider, and ecologic variables were important predictors of RV vaccination. Interventions to increase RV vaccine coverage should consider targeting family physicians.

776. Effects of a Multi-Faceted Program To Increase Influenza Vaccine Coverage among Health Care Workers: A Hospital-Based Cluster Randomized Controlled Trial

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Background: Immunizing health care workers (HCWs) against influenza has proven to protect their patients. Despite recommentations of the World Health Organization and the Dutch Health Council, influenza vaccine uptake among hospital HCWs remains low in the Netherlands

Objectives: To assess the effects of implementing a hospital-based multi-faceted influenza immunization program on vaccine coverage in health care workers (HCW) and on patient morbidity.

Methods: We conducted a cluster randomized controlled trial among all eight University Medical Centers (UMC) of The Netherlands during the influenza seasons of 2009–2010 and 2010–2011. Participants were hospital staff of three intervention (n = 27,900 in 2009), three control (n = 22,451) and two external non-randomized intervention UMCs (n = 16,893), and 3,367 patients admitted to the departments of pediatrics and internal medicine during both influenza epidemics. We offered a vaccination implementation progran to staff of intervention and external UMCs, but not to control UMCs. The primary outcome measure was influenza vaccine coverage among HCW. Secondary outcome measures were work absenteeism and patient morbidity.

Results: In 2009, the coverage of seasonal, first pandemic and second pandemic vaccine was 32.3%, 61.7% and 45.8% in the intervention UMCs. Corresponding figures for control UMCs were significantly lower at 20.4%, 38.0%, and 17.8%, respectively ($p < 0.05$). In 2010, the coverage of the seasonal vaccine was 28.6% and 17.8% in intervention and control UMCs, respectively ($p < 0.05$). During their stay, influenza and/or pneumonia was reduced in patients of intervention UMCs compared to control UMCs (work in progress). Rates of HCWs' absenteeism and influenza testing rates during epidemics were higher in intervention than control UMCs.

Conclusions: Adoption of the program improved the influenza vaccine coverage among hospital staff. An increase in coverage was associated with decreased patient morbidity from influenza and/or pneumonia.

777. Safety of the 2010–2011 Influenza Vaccinations in the Department of Veteran Affairs

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Background: Annually, over 2 million Veterans in the United States (US) are administered influenza vaccinations in the Department of Veterans Affairs (VA). As of the 2010–2011 influenza season, the safety of the influenza vaccine in VA was actively monitored nationally. Possible associations between potential adverse events of interest and influenza vaccination were evaluated at the end of the influenza season.

Objectives: The goal of this study was to determine the safety of the 2010–2011 influenza vaccinations in the US Veteran population treated in the VA.

Methods: VA's integrated automated databases were used to identify Veteran patients who were diagnosed with Guillain-Barre Syndrome (GBS), idiopathic thrombocytopenic purpura (ITP), and Bell's palsy from 10/1/10 to 3/31/11 as identified by ICD-9 code in the VA. The influenza vaccination status for these patients was determined using the VA's Immunization Package database in addition to the integrated automated and prescription databases. Adverse event rates in the risk period (within 1–42 days) were compared to rates in the non-risk period (43 days or after) in terms of incidence rate ratios (IRR) using the self controlled case series method. Only vaccinated cases were included. Seasonality was included to account for possible fluctuation of disease occurrence over the calendar time.

Results: Approximately 2.1 million Veterans received the influenza vaccines (including 42,375 high-dose vaccines) from 10/1/10 to 3/31/11. A total of 38 GBS, 81 ITP, and 575 Bell's palsy post-vaccinated cases were identified. No significant risks for GBS (IRR = 2.07 and 95% CIs = 0.59–7.24), ITP (IRR = 0.71, 95% CIs = 0.32–1.59), and Bell's palsy (IRR = 0.90, 95% CIs = 0.67–1.22) were observed for patients who received the regular dose influenza vaccines. Similarly, no significant increased risk for Bell's palsy (IRR = 1.13, 95% CIs = 0.21–6.02) was observed for patients who received high-dose influenza vaccines. There were no GBS and ITP cases after high-dose vaccines.

Conclusions: There was no evidence of increased risks of GBS, ITP, and Bell's palsy following 2010–2011 influenza vaccinations in the US Veteran population treated in the VA health care system.

778. International Collaborative Case Series Safety Monitoring for Pandemic 2009 H1N1 Vaccines: Estimation of the Risk of Guillain-Barre Syndrome

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Background: The global spread of a novel influenza A (H1N1) virus in 2009 led the World Health Organization (WHO) to declare a pandemic. Vaccine manufacturers worldwide dramatically increased efforts for pandemic H1N1 vaccine production, to make it available to a sizable proportion of the world's population.

Objectives: To investigate the feasibility of globally concerted vaccine safety assessment according to the same protocol as a proof of concept. To test the association between H1N1 vaccination and Guillain Barre Syndrome (GBS) first detected in 1976 with the introduction of the swine flu vaccine.

Methods: The primary outcome of interest was the relative incidence of GBS in the 42 days following vaccination with monovalent adjuvanted and non-adjuvanted pandemic H1N1 vaccine. Cases were identified using hospital or population based health care databases. This included sentinel hospitals and databases of countries choosing to participate. All patients with GBS hospitalized in the selected institutions during the study period were classified according to the Brighton Collaboration case definition of GBS. Data analysis using the self-controlled case series method is being performed with both a pooled data set and a meta-analytic approach.

Results: In total, 546 cases of GBS from 15 countries were included in the study. One hundred and forty-seven subjects with GBS classified at Brighton Collaboration levels 1, 2 or 3 were exposed to pandemic H1N1 vaccine, 78 of

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which were adjuvanted, 61 of which were non-adjuvanted vaccines, and 8 of which had missing adjuvant data. The self-controlled case series analysis is ongoing.

Conclusions: This study demonstrates that a global collaboration with a common protocol is feasible and should allow for estimation of relative incidence of adverse events following exposure to different formulations of the same vaccine.

779. Agreement between Patients' Self-Report and Medical Records for Vaccination: The PGRx Database

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Background: Patients' self-reported vaccine exposure (PS) may be subject to memory errors and other biases. Physicians' prescription records and other medical records (MR) do not capture non-compliance with vaccination. Understanding differences between PS and MR would help researchers interpret studies employing these types of data.

Objectives: To compare PS to MR for influenza, 23-valent pneumococcal and human papillomavirus (HPV) vaccines in the French population.

Methods: The PGRx database relies on a network of over 300 general practitioners (GPs) across France, who systematically recruit an age and sex-stratified sample of patients (≥14 years-old), without reference to their diagnoses or prescriptions. Patients received a structured telephone interview, and an interview guide listing vaccines commonly given. PS for vaccination in the 3 years before recruitment was compared with MR kept by either the physician or the patient. Agreement beyond chance between PS and MR was expressed using bias and prevalence-adjusted kappa statistics (PABAK). Factors associated with disagreement were determined using crude and adjusted logistic regression analyses. Generalized estimating equations were used to analyse influenza vaccines.

Results: Between March 2007 and June 2011, the participating GPs recruited 12,802 patients ≥14 years-old. Concordance between PS and MR was assessed for 7613 patients for whom both sources of information were available. Agreement within 3 years before the recruitment date was substantial for influenza vaccines (PABAK = 0.74), and high for 23-valent pneumococcal vaccines (PABAK = 0.98) and HPV vaccines (PABAK = 0.92). In adjusted analyses, disagreement differed for various sociodemographic and health-related factors.

Conclusions: The PGRx method for drug exposure assessment is a new tool in pharmacoepidemiology that shows substantial to high agreement between PS and MR for exposure to various vaccines. Our finding of high agreement between PS and MR for HPV vaccination status in young women is an important addition to the literature.

780. The Risk of Systemic Lupus Erythematosus Associated with Vaccines: A Case–Control Study in France and Canada

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Background: Studies have suggested that the autoimmune condition systemic lupus erythematosus (SLE) may be triggered by vaccinations through molecular mimicry.

Objectives: This international case–control study investigated relationships between SLE and vaccination in individuals aged 0–60 years. It also focussed on the two most common vaccines in the study population, against influenza and diphtheria-tetanus-pertussis-poliomyelitis (DTPP).

Methods: Between April 2008 and December 2011, 31 specialist referral centers in France and two in Quebec, Canada recruited incident cases of SLE. Cases were diagnosed using an algorithm based on American College of Rheumatology criteria. Controls were recruited from general practice settings in the same geographically diverse areas as the cases. As many controls as possible were matched to each case on: age (< 18 years ± 6 months, ≥18 years ± 24 months), gender, region of residence (northern or southern France or Quebec), recruitment consultation date (± 2 months and within the same season; spring/summer or fall/winter). Vaccinations and

other potential risk factors for SLE were assessed in a standardized telephone interview. The interviewer was blind to case/control status. Cases and controls were compared for vaccination in the 12 and 24 months before the index date, using odds ratios (OR) from conditional logistic regression.

Results: One hundred and eleven eligible cases of SLE were recruited and 99 were included in the analysis. Of 7869 eligible controls were recruited and 692 were matched to cases. Twenty cases (20.2%) and 174 controls (25.1%) received at least one vaccination within 24 months before the index date. Cases and controls were similar for the proportions vaccinated in the previous 12 or 24 months (adjusted OR for 24 months 0.78, 95% confidence interval 0.41, 1.47). This conclusion did not change when vaccines against influenza and DTPP were analyzed separately.

Conclusions: This systematic case–control design is well-suited to study rare disorders such as SLE and few such studies have been conducted. We found no evidence of an increase in the risk of SLE following vaccination.

781. Guillain-Barré Syndrome and Pandemic Influenza A(H1N1) 2009 Vaccines: Meta-Analysis of Observational Risk Estimate Studies from 2010 and 2011

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Background: Several countries and one European concerted study have now reported on the association between the pandemic H1N1 vaccine and the risk of GBS. This is the result of active surveillance programs started alongside the 2009/2010 vaccination campaign due to the previously observed association during the 1976 swine flu vaccination campaign in the USA.

Objectives: To conduct a meta-analysis of observational studies assessing the association between the A(H1N1)pdm09 vaccine and GBS.

Methods: In a systematic literature review, all English publications on A(H1N1)pdm09 vaccination and GBS between January 2010 and December 2011 were retrieved from Medline and EMBASE. Abstracts were reviewed for in-and exclusion criteria. Final assessment was done by two persons independently. Relative risk ratios (RR) were pooled applying a meta-analytic approach with a random effects model.

Results: The systematic literature search resulted in 407 publications. The screening process identified 13 potentially eligible studies. Following review four studies qualified for a meta-analysis. The following RR were reported: Andrews, UK, 2011, VACCINE, RR = 1.1 (CI 95%, 0.4–2.2); Dieleman, EU, 2011, BMJ, RR = 1 (CI 95%, 0.3–2.7); Grimaldi-Bensouda, FR, 2011, Am J Epidemiol, RR = 2.3 (0.7–8.2); and US CDC 2010, USA, MMWR, RR = 1.8 (CI 95%, 1.1–2.6). The pooled adjusted RR of these four studies was 1.6 (CI 95%, 1.2–2.1), homogeneity p = 0.5. Although the US study should be considered preliminary and final results are being published soon. Lee et al., USA, 2011, in *Am J Prev Med.*, reported a log likelihood ratio of 1.56. We did not include this study, because CIs are lacking. In the UK, in FR, and in the EU study predominantly adjuvanted vaccines have been administered. If restricted to countries where adjuvanted vaccines were used, the pooled RR was 1.2 (CI 95%, 0.7–2.1), homogeneity p = 0.5.

Conclusions: We showed that the studies have consistent RR and that there is at most a minimal increased risk of GBS after A(H1N1)pdm09 vaccination. The US studies of the risk of GBS following non-adjuvanted A(H1N1)pdm09 vaccines are currently being finalized.

782. Evaluating the Safety of 2009 H1N1 Influenza Vaccine Using a Claims-Based Health System

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Background: Safety monitoring and evaluation is a critical component of vaccination programs. As a part of its monitoring and evaluation activities for influenza vaccines, the Centers for Disease Control and Prevention (CDC) conducted a retrospective evaluation of the safety of the H1N1 influenza vaccine administered during the 2009 influenza season using a large U.S. claims-based data environment (OptumInsightTM).

Objectives: To use claims data to assess the associations between the 2009 H1N1 influenza vaccine and several prespecified health outcomes.

Methods: Patients ages 6 months and older with a claim for H1N1 vaccine during the 2009 influenza season were included in the analysis. We implemented different analytic approaches for the pre-specified outcomes depending on the number of cases of that outcome. For Bell's palsy, other cranial nerve disorders, central demyelinating disease, Guillian-Barre Syndrome (GBS), disorders of the peripheral nervous system and neuropathy, and seizures, we used a Self-Controlled Risk Interval (SCRI) design. GBS and seizure events were confirmed through medical record review. A Poisson regression analysis was conducted for ataxia, encephalitis/myelitis/transverse myelitis, hemorrhagic stroke, narcolepsy and cataplexy, ischemic stroke, anaphylaxis and other allergic reactions (including angioneurotic edema and urticaria). Patients with seasonal

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influenza vaccination claims during the 2005–2008 influenza seasons were used as a historical comparison.

Results: A total of 538,257 doses of H1N1 influenza vaccine were captured in the claims data during the 2009 influenza season. We found no increased risk for the prespecified outcomes following H1N1 influenza vaccination, although the number of doses may have been insufficient to detect rare outcomes. After chart confirmation, there was 1 GBS case in the risk window and 1 case in the control window. There were 2 chart-confirmed seizure cases in the control window and 0 in the risk window.

Conclusions: This study did not find increased risk for the pre-specified outcomes following 2009 H1N1 influenza immunization.

783. Active Monitoring of Adverse Events during an MF59®-Adjuvanted H5N1 Influenza Vaccination Campaign in Taiwan

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Background: In March 2011, Taiwan began a voluntary prepandemic vaccination program to immunize at-risk adults with an MF59®-adjuvanted H5N1 vaccine (Aflunov®). We conducted a pilot study to actively monitor adverse events following immunization (AEFIs).

Objectives: To identify and quantify the occurrence of adverse events among Aflunov® recipients.

Methods: From March 1 to September 30, 2011, Aflunov® recipients voluntarily signed up for study participation through the toll-free "1922" hotline within 72 hours of vaccination. Data were collected from participants at enrollment on demographics, immunizations, chronic medical conditions, and contact details. We conducted telephone interviews of each participant at 7–10 and 21–24 days after vaccination. Questions were asked about solicited injection site reactions (pain, erythema, swelling/induration, feeling of warmth, pruritus, and hematoma), solicited systemic reactions (headache, fatigue, pyrexia/sweating/chills, myalgia, arthralgia, and lymphadenopathy), and serious adverse events (SAEs) that occurred through the time of their vaccinations or from the last interviews; unsolicited AEFIs were filled in as free texts.

Results: Two hundred ninety-two persons registered as participants (184 female, median age 39 years [range 20–77]); 270 and 263 interviews had been completed at 7–10 and 21–24 days. At 7–10 days, 127 (47%) respondents reported injection site reactions and 79 (29%) reported systemic reactions. The most frequently reported solicited injection site and systemic reactions were pain (n = 109, 40%) and fatigue (n = 40, 15%), respectively. Females (odds ratio [OR] 2.06, 95% CI 1.18–3.63), nonelderly adults aged 18–59 years (OR 3.08, 95% CI 1.11–9.45), and subjects receiving their first dose of Aflunov® (OR 2.16, 95% CI 1.22–3.86) were more likely to report an adverse event within the first 7–10 days postvaccination. None of the AEFIs reported were SAEs.

Conclusions: Most adverse events to Aflunov® were anticipated but varied with gender, age, and vaccination status. This telephone-based surveillance can be expanded to rapidly collect AEFIs in large campaigns involving influenza or other emerging vaccines.

784. Abstract withdrawn by author.

785. Report on BCG Vaccine-Associated Suppurative Lymphadenitis

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Background: In 2009–2010, pediatricians observed an increase in BCG suppurative lymphadenitis. Similar increase was reported overseas. Literature showed that factors such as patient's age, administration route, strain and viability of vaccines may be associated with the adverse event. The Department of Health (DH) conducted a study to investigate whether there is a genuine increase and the possible causes.

Objectives: To study the incidence of BCG suppurative lymphadenitis from 2003 to 2010 and to analyze any factor related to the increase.

Methods: DH reviewed the discharge summaries of public hospitals with relevant ICD codes. Details related to patient, vaccine and vaccination records were collected by reviewing clinical records and interviews. Cases of suppurative lymphadenitis were analysed. Laboratory information on colony forming units (CFUs) of different vaccine batches were reviewed. Samples of vaccine were tested. Storage conditions in some public hospitals providing BCG vaccination were inspected.

Results: A total of 64 records of patients with BCG suppurative lymphadenitis were identified. The incidence per 10,000 doses revealed increase in from 0.43 in 2003 to 2.85 in 2010. There has been one BCG vaccine manufacturer supplying the same strain since 2001. Mycobacterial growth and viability tests showed the samples complying with specifications. Hospitals inspections revealed no irregularity of storage facility and cold delivery chain. Host related factors and CFU counts of different vaccine batches are being analysed for factors related to the increase.

Conclusions: Increase in BCG suppurative lymphadenitis has been observed in Hong Kong and other places. Retrospective review of clinical records provides important information for surveillance to confirm the association of risk factors.

786. Tolerability of a Combined dTP-IPV-Hib- and a 7- or 10-Valent Pneumococcal Vaccination in Infancy – Work in Progress

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Background: In March 2011, the National Immunization Program in the Netherlands changed from a 7-valent to a 10-valent pneumococcal vaccine for infants. While continuous monitoring of adverse events based on a passive reporting system gives insight in changes of potential serious adverse events, this ongoing study assesses changes of more common, milder adverse events.

Objectives: To gain insight in the occurrence of adverse events after the NIP is changed from using a 7-valent to a 10-valent pneumococcal vaccine for infants.

Methods: Questionnaires on local and systemic reactions were distributed 1 week before and 1 week after the first three doses in infancy, to two cohorts of about 12,000 parents of infants who received dTP-IPV-Hib- and 7- (Cohort-7) or 10-valent pneumococcal (Cohort-10) vaccination. Frequencies of side effects at the dTP-IPV-Hib- and pneumococcal site within 1–7 days were assessed.

Results: In Cohort-7 local reactions occurred in 30.6%, 37.7% and 29.0% of the children within 7 days after the first three doses, respectively. In Cohort-10 the frequency of local reactions after the three doses was slightly higher (47.5%, 41.4% and 30.3%). For both cohorts, no differences were seen in local reactions between the dTP-IPV-Hib- and the pneumococcal injection site. Severe local reactions were less common for children in Cohort-10 compared to children in Cohort-7. In Cohort-7, systemic events due to vaccination occurred in 35.5%, 32.4% and 26.9% of the children within 7 days after the three vaccinations, with a changed sleeping pattern as the most frequently reported. Higher frequencies of systemic events due to vaccination were found in Cohort-10 (53.2%, 48.4% and 32.0%, respectively), with crying as most frequently reported.

Conclusions: The change from 7-valent to 10-valent pneumococcal vaccination resulted in higher frequencies of self-reported local and systemic events, although for severe local reactions an opposite trend was seen. The difference between the two cohorts is less pronounced after the second and third vaccination. In spring 2012 we will be able to study whether this smooth down will persists after the fourth vaccination.

787. Risk of Febrile Seizures in Children Following Trivalent Inactivated Influenza Vaccine in the Vaccine Safety Datalink Project, 2010–2011

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Background: In fall 2010 in the Southern Hemisphere, increased risk of febrile seizures was noted in young children in Australia in the 24 hours after trivalent inactivated influenza vaccine (TIV) manufactured by CSL Biotherapies.

Objectives: During the 2010–2011 season, weekly surveillance was conducted for febrile seizures in the 0–1 days following first dose TIV in 206,174 children ages 6–59 months in the Vaccine Safety Datalink, a collaboration between the Centers for Disease Control and Prevention and 10 medical care organizations.

Methods: Weekly surveillance was conducted with self-controlled risk interval and current vs. historical vaccinee designs. Sequential statistical methods were used to account for repeated analyses. Signals for seizures based on computerized data were identified in mid November 2010 with the current vs. historical design and in late December 2010 with the self-controlled risk interval design. Signal evaluation was conducted with chart-confirmed febrile seizure cases using the self-controlled risk interval design.

Results: The incidence rate ratio (IRR) for TIV adjusted for concomitant 13-valent pneumococcal conjugate vaccine (PCV13) was 2.4 (95% CI 1.2, 4.7) while the IRR for PCV13 adjusted for concomitant TIV was 2.5 (95% CI 1.3, 4.7). The risk differences (RD) varied by age and receipt of concomitant PCV13, with the highest estimates at 16 months (13 per 100,000 doses for TIV without concomitant PCV13, 14 per 100,000 doses for PCV13 without concomitant TIV, and 45 per 100,000 doses for concomi-

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tant TIV and PCV13) and the lowest estimates at 59 months (one per 100,000 doses for TIV without concomitant PCV13, one per 100,000 doses for PCV13 without concomitant TIV, and four per 100,000 doses for concomitant TIV and PCV13).

Conclusions: An elevated risk of febrile seizures in the 0–1 days following first dose TIV was identified during the 2010–2011 season in children ages 6–59 months. The magnitude of RD estimates was dependent on age and concomitant PCV13 vaccine, with the highest RDs at 16 months and the lowest RDs at 59 months. Results should be placed in a benefit-risk framework to maximize population health benefits.

788. Prevalence of Urinary Tract Infections and Pharmacotherapy Use in Pregnancy – National Birth Defects Prevention Study (NBDPS), 1997–2007

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Background: Urinary tract infections (UTIs) affect 20–25% of pregnant women in the United States. Unmanaged UTIs can lead to adverse pregnancy outcomes; however, studies have suggested associations with early pregnancy use of some antibacterials and specific birth defects.

Objectives: To determine the prevalence of UTIs and the use of related pharmacotherapy in early pregnancy.

Methods: Data were obtained from the NBDPS, a multisite, population-based case–control study of risk factors for birth defects. Data from computer assisted telephone interviews with mothers of cases, identified through birth defect surveillance systems, and controls, randomly selected from the same source population and time period as cases, were used to estimate the prevalence of UTIs and use of specific medications from the month before conception to the end of the first trimester. Chi-square tests were used to assess differences between mothers of cases and controls.

Results: The prevalence of any self-reported UTI was significantly greater in case mothers, 21.3% (4940/23,161), compared to control mothers, 19.6% (1655/8450) ($p < 0.001$). However, the proportion of these UTIs that were diagnosed by a physician did not differ between case (4702/4940, 95.2%) and control mothers (1570/1655, 94.8%), nor did the proportion who used any pharmacological treatment (n = 4134/4702, 87.9% for case mothers and n = 1401/1570, 89.2% for control mothers) ($p = 0.13$). More case mothers than control mothers used amoxicillin (40.7% vs. 36.6%) ($p < 0.001$) and trimethoprim/sulfamethoxazole (TMP/SMX) (18.6% vs. 13.3%) ($p < 0.001$). The use of nitrofurantoin did not differ between case and control mothers (24.4% vs. 25.4%) ($p = 0.45$).

Conclusions: The prevalence of UTIs was observed to be higher in case mothers compared to control mothers. Although the use of any pharmacotherapy did not differ between case and control mothers, the use of amoxicillin and TMP/SMX was significantly greater in case mothers. Further investigation will assess potential associations between these medications and specific birth defects.

789. Sulfamethizole in Pregnancy and the Risk of Neonatal Jaundice or Kernicterus – A Nation-Wide Register Based Cohort Study

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Background: Sulfamethizole is in Denmark used for treating uncomplicated urinary tract infection. The recommendation is not to use sulfamethizole in late pregnancy due to risk of neonatal jaundice and kernicterus in the offspring.

Objectives: To investigate the association between maternal use of sulfamethizole close to birth and the risk of neonatal jaundice and kernicterus in the offspring.

Methods: We conducted a nationwide population based retrospective cohort study using nationwide Danish registers. All Danish women giving birth between 1995 and 2007 were included from the Danish Fertility Database. Women redeeming a prescription on sulfamethizole up to 28 days before giving birth were identified from the National Prescription Register. The primary outcome was the number of children diagnosed with neonatal jaundice and/or kernicterus identified in the National Hospital Register. Logistic regression were used to estimate odds ratios (OR) of neonatal jaundice. We adjusted for maternal age, education, household income, period of conception, gestational age, and parity.

Results: We identified 841,900 births in the study period. Out of 1,823 neonates exposed to sulfamethizole up to 28 days before birth, 197 developed neonatal jaundice. None developed kernicterus. OR of developing neonatal jaundice after in utero exposure to sulfamethizole 28 days before birth was 2.35 (95% CI 2.02–2.72). Adjusted for maternal age, education, household income, parity and period of conception, OR decreased to 2.29 (95% CI 1.97–2.67). Further adjustment for gestational age eliminated OR to 1.03 (95% CI 0.86–1.22). When narrowing the exposure time of sulfamethizole to 1–7 days prior to birth OR was the same.

Conclusions: Women redeeming a prescription of Sulfamethizole close to birth do not have an increased risk of hav-

ing children with neonatal jaundice or kernicterus. Neonatal jaundice seems to be related to prematurity which is probably caused by the maternal urinary tract infection.

790. Antimalarial Drugs and the Risk for the Pregnant Women and Fetuses: Review of the Literature

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Background: WHO recommends the use of artemisinin combination based therapies (ACT) and quinine + clindamycin for the treatment of malaria in pregnancy. Pregnant women are inadvertently exposed to all antimalarials during gestation. Very little is known about the safety of these drugs during this period.

Objectives: This literature aims to provide an update on the risks associated with gestational use of antimalarial during pregnancy.

Methods: A systematic search in PubMed was performed using the following keywords: (''antimalarial'' [MeSH Terms] OR ''Antimalarials'' [All Fields] OR ''Antimalarials'' [Pharmacological Action]) AND (''pregnancy'' [MeSH Terms] OR ''pregnancy'' [All Fields]) AND (''Human'' [MeSH Terms] AND (''1966/01/01'' [PDAT]: ''2012/04/30'' [PDAT]). Other than having a comparative study, there were no other exclusion criteria. A systematic review was performed on all studies identified.

Results: The literature review identified 70 studies. The majority were on antifolates (31.4%), and artemisinin combination therapies (17.14%). Data on quinine use during pregnancy are reassuring. The risk of mefloquine during the 1st trimester of pregnancy is controversial. To date there is no evidence on the safety of amodiaquine in pregnancy in the literature. Antifolates as a group reported an increased risk of birth defects (RR = 3.4 ; 95% CI, 1.8–6.4) during the second and third trimester of pregnancy. The safety of artemisinin and its derivatives is not yet clearly established.

Conclusions: The risk of antimalarials in pregnancy, mainly in the first trimester of pregnancy, is not widely reported in the literature. However, antifolates should clearly be avoided.

791. Risks and Benefits of the Use of Metronidazole during Pregnancy: A Review of the Evidence

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Background: Metronidazole is an anti-infective drug used against infections, such as tricomoniasis and bacterial vaginosis. Given that these conditions are known risk factors for preterm birth, this agent is potentially useful during pregnancy. However, available data on the risk of metronidazole during gestation is contradictory and controversial.

Objectives: To present an overview of the evidence concerning the association between the use of metronidazole during pregnancy and the risk of preterm delivery and birth defects.

Methods: We systematically searched PUBMED and EMBASE databases for etiologic studies with data on human subjects that examined the association between gestational exposure to metronidazole and the risk of preterm birth or birth defects. Combinations of the following MeSH terms were used: metronidazole or prematurity or preterm birth or congenital malformations or birth defects or anomalies or pregnancy or antibiotics or bacterial vaginosis or trichomoniasis. All relevant articles, published in English or French between 1964 and 2010, were reviewed. If authors did not report the odds ratio (OR) for preterm birth or birth defects, crude ORs and 95% confidence intervals (CI) were calculated.

Results: Seventeen studies that investigated the association between exposure to oral metronidazole during pregnancy and the risk of preterm birth were included. Twelve of these studies were randomized clinical trials. We also retrieved 13 studies that investigated the association between exposure and the risk of birth defects. Ten of these were cohort studies; one was a case–control study and two were meta-analysis.

Conclusions: Treatment with metronidazole is effective against bacterial vaginosis and tricomoniasis during pregnancy, and offers no teratogen risk for babies of exposed women. Benefit of metronidazole in the reduction of preterm birth rates was demonstrated only for the combination of this agent with other antibiotics. More evidence is needed on the risk of birth defects, when metronidazole is used in association.

792. Safety of Macrolide Antibiotics Use during Pregnancy

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Background: Macrolide antibiotics are used in pregnant women diagnosed with infections (vaginal, respiratory)

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and premature rupture of membranes. Previous studies were limited by lack of data on medical termination of pregnancy, and by limited information on 3rd trimester exposure.

Objectives: To evaluate the safety of macrolide antibiotics use during early and late pregnancy.

Methods: We conducted a population based historical cohort study including cases of medical terminations of pregnancy. A unified database was created by linking a database of medications dispensed from 1999 to 2009 to women registered in "Clalit" HMO, southern district of Israel, with databases containing maternal and infant hospitalization records from the district hospital, Soroka Medical Center. Rates of adverse fetal effects in macrolides exposed and unexposed pregnancies were compared. Multivariate logistic-regression models were constructed to identify independent risk factors associated with adverse outcomes for the fetus. Associations between exposure to macrolides during the 1st trimester and major malformations were assessed, adjusting for parity, maternal age, ethnic group, maternal diabetes and year of pregnancy. Associations between exposure to macrolides during the 3rd trimester and other adverse outcomes such as perinatal mortality were also assessed, adjusting for the same factors mentioned above, and for potential independent risk factors associated with each tested outcome (e.g., maternal smoking status for low birth weight).

Results: A total of 105,492 pregnancies were included in our research, of which 1,112 pregnancies were terminated for medical reasons. Exposure of 1,033 infants and abortuses to macrolides during the 1st trimester was not associated with an increased risk of major malformations (adjusted OR 1.08; 95% CI = 0.84–1.38). Similarly, exposure of 959 infants to macrolides during the 3rd trimester was not associated with increased risk of perinatal mortality, premature delivery, low birth weight, or low APGAR scores.

Conclusions: Intrauterine exposure to macrolides was not associated with increased risk for major malformations, perinatal mortality, or morbidity.

793. Prevalence of Exposure to Mebendazol and Pyrvinium during Pregnancy – A Nationwide Cohort Study

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Background: Mebendazol and Pyrvinium are, in Denmark, used to treat pinworm infections. This infection spreads easily between family members, and as a result it is recommended to treat all family members. There is limited data concerning the prevalence of exposure to Mebendazole or Pyrvinium during pregnancy. The purpose of this study is therefore to analyze the prevalence of exposure during pregnancy as well as changes in prescription patterns in relation to pregnancy.

Objectives: To determine the prevalence of exposure to Mebendazole and Pyrvinium during pregnancy in a nationwide cohort.

Methods: All live births in Denmark between 1997 and 2007 were identified using The Danish Fertility Database. Redemption of prescriptions for Mebendazole (ATC P02CA01) and Pyrvinium (ATC P02CX01) were identified through The Danish National Prescription Registry. Data management were all performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results: We identified 718,900 births between 1997 and 2007. We found 4,705 (0.65%) mothers redeeming a prescription for Pyrvinium or Mebendazole during pregnancy; 1,606 (0.22%) for Pyrvinium, 2,575 (0.36%) for Mebendazole, and 534 (0.07%) for both drugs. We observed a 50% decrease of exposure to Mebendazole, and a 12-fold increase in exposure to Pyrvinium during the first trimester, compared to the 3 months before conception.

Conclusions: We analyzed the prevalence of exposure to Mebendazole and Pyrvinium, and changes in connection to pregnancy start, and identified a considerable amount of exposed women. The observed shift toward use of Pyrvinium in the first trimester reflects the recommendation to prefer this drug in pregnancy. Information concerning pregnancy outcomes associated with exposure to these drugs is limited. Further studies are therefore needed to ascertain the safety of exposure to Mebendazole and Pyrvinium during pregnancy.

795. Pregnancy Prevention Programme of Isotretinoin and the Adherence by Dutch Community Pharmacists

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Background: Isotretinoin, indicated for the treatment of severe acne, contains a Pregnancy Prevention Programme (PPP) because of its teratogenicity. Pharmacists should control the correct distribution of isotretinoin, especially to women of childbearing potential.

Objectives: The aim of this survey was to investigate pharmacist's compliance with the PPP as one of the stakeholders in the performance of this programme.

Methods: An online questionnaire was sent to community pharmacists, members of the Dutch Association of Pharmacists in a newsletter. Later on, it was sent to pharma-

cists of the research group of the Association (n = 556) by e-mail. Descriptive statistics were performed.

Results: Demographic characteristics of the responding pharmacists: 61% were female and 68% was between 25 and 45 years of age. A total of 148 pharmacists participated in this survey. The response of the research group was 20% (109 out of 556), the response rate over the total group could not be determined. The majority of all responders (82%) receive an alert for restriction to supply for 30 days, however 36% stated to strictly adhere to this restriction. With first delivery of isotretinoin: – 86% of the pharmacists provided additional information on teratogenicity, – 62% provided this information especially to women of childbearing potential, – 85% of the pharmacists provided information on contraceptive use, and – 82% checked their system on prescriptive contraceptives for this specific patient. Thirty-two percent of the pharmacists only accepted prescriptions from dermatologists. Most of the pharmacists (74%) considered the prescriber primarily responsible for the performance of the PPP. Pharmacists considered themselves responsible for the surveillance of the prescription restrictions and eventual prescriptive contraceptive methods.

Conclusions: A majority of Dutch pharmacists adhered to the performance of the isotretinoin PPP with some exceptions. First delivery of isotretinoin is clearly the time to provide information on the teratogenicity and contraception. Pharmacists considered the monitoring of prescription restriction mainly as their responsibility.

796. Progesterone in Pregnancy: A Comparative Study in EFEMERIS Database

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Background: Progesterone is a naturally hormone used in prevention of spontaneous abortion and *in vitro* fertilization. An association between progestin exposure during pregnancy and congenital anomalies (mainly hypospadias) has been reported in three studies. In contrast, other authors could not identify an increased risk.

Objectives: The present study investigates potential teratogenic risk of progesterone in pregnancy.

Methods: EFEMERIS is a database including prescribed and delivered drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnostic Centre). Women delivered from July 1st 2004 to June 30th 2008 in Haute-Garonne and registered in the French Health Insurance Service were included into EFEMERIS database. We compared pregnancy outcomes and newborn health between women exposed to progesterone during organogenesis and non exposed women. Malformations were classified according to Eurocat classification.

Results: Of the 1,519 (3.8%) newborns exposed during organogenesis to progesterone were compared with 38,464 controls (non exposed newborns). The average age of the mothers was 32.6 ± 4.9 years in exposed group and 30.1 ± 5.0 in the control group ($p < 10^{-4}$). Prematurity rate was higher in the group of newborns exposed to progesterone than in controls (10.9% vs. 4.8%, $p < 10^{-4}$). In the group of newborns whose mother had a prescription of progesterone during organogenesis, 47 (3.1%) had a malformation vs. 872 (2.3%) in the control group (p = 0.04). Exposed newborns had more nervous system malformations than controls (6.6‰ vs. 2.0‰, OR = 3.3 [1.7–6.3]). In contrast, the risk of urinary malformations was similar in the two groups (4.6% in exposed group vs. 4.8% in controls, p = 0.9).

Conclusions: The present study found an association between progesterone prescription during organogenesis and birth defects, i.e., nervous system anomalies.

797. Exposure to Enoxaparin during the First Trimester of Pregnancy and the Risk of Major Malformations

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Background: Enoxaparin (LMWH) is the drug of choice for anticoagulation therapy during pregnancy. Despite the abundance of studies investigating the effectiveness of enoxaparin during pregnancy, no study examined its fetal safety.

Objectives: To evaluate the fetal safety following intrauterine exposure to enoxaparin during the first trimester of pregnancy.

Methods: A population based retrospective cohort study of all women registered in the "Clalit" health maintenance organization in Southern Israel, was conducted. A computerized database of medications dispensed from 1998 to 2009 linked with two computerized databases

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containing maternal and infant hospitalization records. The study included live birth, stillbirths and medical pregnancy terminations. The following confounders were controlled for: maternal age, ethnicity, folic acid intake, parity, year of birth or medical pregnancy termination, smoking status and maternal morbidity (including pre gestational diabetes). Multivariate Logistic regression model was used to examine the adjusted fetal risk of malformations after exposure to enoxaparin during the first trimester of pregnancy.

Results: A total of 112,769 infants were born during the study period. Of 109,794 of them were singletons; 1,173 women had medical pregnancy termination.

Among the study cohort, 438 women were exposed to enoxaparin during first trimester of pregnancy. Exposure to enoxaparin was not associated with increased risk of major malformations (adjusted OR 1.08; 95% CI = 0.73–1.57), low birth weight (adjusted OR 0.84; 95% CI = 0.49–1.43) and low apgar score (adjusted OR 0.76; 95% CI = 0.55–1.06).

Conclusions: Intrauterine exposure to enoxaparin during the first trimester of pregnancy was not associated with increased risk for major malformations, nor other investigated adverse birth outcomes. The drug can be used safely during gestation.

798. Increasing First Trimester Use of Opioid Analgesics

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Background: Use of opioid analgesics has increased dramatically in recent years, but there is little information about whether use of these medications during pregnancy has increased. Given that opioids may pose a risk for the developing fetus, information on potential early fetal exposure is urgently needed.

Objectives: To quantify the prevalence of opioid analgesic use during the first trimester among pregnant women enrolled in Tennessee Medicaid increased from 1995 to 2009.

Methods: Retrospective cohort study using Tennessee Medicaid, birth certificate, and fetal death certificate data to identify pregnancies among women enrolled in Tennessee Medicaid from 1995 to 2009. Filled prescriptions for medications of interest were considered to represent first trimester exposures if the prescription was filled between the last menstrual period and the subsequent 89 days or the days supply for a prescription filled before pregnancy overlapped into pregnancy. The main outcome measure was any first trimester prescription opioid analgesic use. Trends over the study period were tested using Poisson regression.

Results: Of the 268,987 pregnancies were included in the analytic cohort. During the entire study period, 14.50% of pregnancies filled at least one prescription for an opioid analgesic during the first trimester. Use increased from 8.58% of pregnancies in 1995 to 20.06% of pregnancies in 2009. After adjusting for maternal characteristics, the prevalence of any first trimester use in 2009 was 2.31 times greater than in 1995 (95% CI = 2.17–2.46). Older, white, non-Hispanic mothers with less than a high school education and one or more prior pregnancies were more likely to have filled at least one prescription for an opioid analgesic during the first trimester.

Conclusions: First trimester use of opioid analgesics increased from 1995 to 2009 among Tennessee Medicaid-insured pregnant women. There is a critical need to further examine the consequences of early fetal exposure to these medications.

799. Major Malformations Following Exposure to Nonsteroidal Antiinflammatory Drugs during the First Trimester

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Background: Non aspirin non-steroidal anti-inflammatory drugs (NSAIDs) are among the most common medicines used by pregnant women. Published data are controversial regarding fetal safety following intrauterine exposure to NSAIDs.

Objectives: To evaluate the fetal safety following intrauterine exposure to non aspirin NSAIDs during the first trimester of pregnancy.

Methods: A computerized database of medications dispensed from 1998 to 2009 to all women registered in the "Clalit" health maintenance organization in Southern

Israel, was linked with two computerized databases containing maternal and infant hospitalization records. Also, medical pregnancy terminations data were analyzed. The following confounders were controlled for: parity, maternal age, ethnicity, maternal pre gestational diabetes, maternal inflammatory disease and year of birth or medical pregnancy termination. First trimester exposure to non-selective cyclooxygenase (COX) inhibitors and to selective COX2 inhibitors as groups, and to individual drugs was analyzed.

Results: There were 110,783 pregnancies during the study period; 109,544 singleton births and 1,239 medical pregnancy terminations. In total, 5,267 mothers were exposed to non aspirin NSAIDs during the first trimester of pregnancy: 5,153 to non-selective COX inhibitors and 114 to COX2 selective inhibitors. Exposure to NSAIDs in the first trimester, as groups (non-selective COX and selective COX2 inhibitors) and as individual drugs, was not associated with an increased risk of major congenital malformations in general (adjusted OR = 1.07; 95% CI 0.96–1.21, and adjusted OR = 1.40; 95% CI 0.70–2.78 for non-selective and for selective COX2 inhibitors, respectively).

Conclusions: Intrauterine exposure to non aspirin NSAIDs was not associated with increased risk for major congenital malformations. Further studies are needed to assess the risk for malformations after exposure to COX2 selective inhibitors.

800. Patterns of Antidepressant and Antipsychotic Use during Pregnancy

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Background: Most studies on drug utilization during pregnancy report cross-sectional, trimester-specific prevalences of drug use; few studies follow individual women throughout pregnancy and evaluate longitudinal changes in medication use.

Objectives: To describe antidepressant and antipsychotic use by trimester, and longitudinally along individual pregnancies.

Methods: All women in the General Practice Research Database's Mother-Baby Link (which consists of pregnancies ending in live births) with delivery between 1989 and 2010, who were continuously enrolled from 6 months before pregnancy to 3 months after delivery were included in the study cohort (n = 421,645). The gestational periods of interest were 3 months before pregnancy (T0), each trimester of pregnancy (T1–T3), and 3 months after delivery (T4). Drug use prevalence was calculated as the number of all pregnancies issued a prescription for antidepressants or antipsychotics (excluding prochlorperazine) in each of T0–T4 over all cohort pregnancies. In each pregnancy, prescriptions for capsules/tablets in T0 and T3 were compared to identify these longitudinal treatment patterns: discontinuation, simplification (some drugs discontinued or dose lowered), no treatment change, intensification (drugs added to prior treatment or dose increased), and start of treatment.

Results: Antidepressant use in T0 through T4 was 4.69%, 2.81%, 1.31%, 1.34%, and 5.46%, respectively. Of 19,774 T0 antidepressant users, 79.57% discontinued treatment, 5.13% simplified treatment, 9.06% did not change treatment, and 2.19% intensified treatment. Of 0.40% of non-users in T0 started antidepressants by T3. Antipsychotic use in T0 through T4 was 0.15%, 0.13%, 0.08%, 0.07% and 0.15%, respectively. Of 639 T0 users, 72.30% discontinued treatment, 7.51% simplified treatment, 11.11% did not change treatment, and 4.07% intensified treatment. Of 0.03% of non-users in T0 started antipsychotics by T3.

Conclusions: Both cross-sectional and longitudinal analyses identified the post-conception decrease in antidepressant and antipsychotic use. Longitudinal follow-up additionally allowed us to describe several treatment patterns that usually stay unrecognized.

801. The Use of Antiepileptic Drug during Pregnancy in Finland 1996–2008

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Background: The use of maternal antiepileptic drugs (AED) cannot always be discontinued before pregnancy. Individual old-generation AEDs are established teratogens, whereas the safety of several new-generation AEDs remains unclear due to lack of large studies.

Objectives: To evaluate the pattern of reimbursed AED purchases during pregnancy in Finland between 1996 and 2008, using nationwide population-based register data.

Methods: Information on born children (n = 751,139) in Finland during 1996–2008 was obtained from the Medical Birth Register and linked to information on AED purchases obtained from the reimbursement database of the Social Insurance Institution.

Results: A total of 4,202 infants (0.55%) were exposed to AEDs 1 month before or during pregnancy, and mainly in monotherapy (86.6%). Overall, the most frequently used AED in pregnancy during the whole study period was carbamazepine (CBZ, 35.5% of AED exposed) but it's use declined significantly during the study years (from 0.3% to 0.1% in all parturients and from 56.9% to 16.1% in AED-exposed parturients), while the use of lamotrigine (LTG) clearly increased (from 0.0% to 0.2% in all parturients and from 0.4% to 20.4% in AED-exposed). A slight increase in the use of valproate (VPA) was observed in all parturients (from 0.1% to 0.2%) but among AED

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exposed the proportion of VPA -exposed remained similar between 1996 (26.7%) and 2008 (25.8%).

Conclusions: The use of VPA during pregnancy increased between 1996 and 2008 in Finland and it was the most frequently used AED in the end of the study period. The well-established teratogenic and neurotoxic risks related to VPA use during pregnancy should be acknowledged when prescribing this AED to women of childbearing age, and switching to safer alternatives should be considered whenever possible.

802. Antiepileptic Drug Use among Pregnant Women in the U.S., 2001–2007: A MEPREP Study

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Background: Antiepileptic drug (AED) use has been increasing in the general population. Yet, little is known about the extent to which AEDs are used in pregnancy, particularly for newer agents.

Objectives: To assess whether AED use has increased among pregnant women in the U.S., 2001–2007.

Methods: We analyzed data from MEPREP, a collaborative effort between the U.S. FDA and 11 U.S. health plan-affliated research institutions. We identified live-born deliveries (1/1/2001–12/31/2007) among health plan members aged 15–45 years on delivery date. Pregnancy exposure to AEDs was determined through outpatient pharmacy dispensing files. First-generation AEDs included those available for clinical use before 1993; other agents were considered second-generation AEDs. Information on sociodemographic and medical/reproductive factors was obtained from linked birth certificate files. Maternal diagnoses were identified based on ICD-9 codes, and were classified into five groups (any epilepsy, psychiatric disorder, pain disorder, neuromuscular disorder, and sleep disorder). Prevalence was defined as the number of AED-exposed deliveries per 1,000 qualifying deliveries.

Results: Among 585,615 deliveries, 11,611 (˜2%) included at least one AED prescription during pregnancy. The prevalence of AED use increased between 2001 (15.7 per 1,000 deliveries) and 2007 (21.9 per 1,000 deliveries), driven primarily by increased use of second-generation AEDs (1.6 per 1,000 deliveries in 2001 to 8.9 per 1,000 deliveries in 2007). The use of first-generation drugs remained relatively unchanged during the study period (range 14.6 to 16.2 per 1,000 deliveries). Psychiatric, epileptic, and pain disorders were the most prevalent diagnoses among AED users. Approximately 13% of AED-exposed deliveries involved the use of AED combinations primarily concomitant use of first- and second-generation drugs.

Conclusions: Between 2001 and 2007, there was a fivefold increase in the use of second-generation AEDs. Nearly one in eight AED-exposed deliveries involved concomitant AED use. Additional investigations of the reproductive safety of newer AEDs may be needed.

803. Antipsychotic, Anticonvulsant and Lithium Use during Pregnancy

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Background: There is concern that fetal exposure to antipsychotics and anticonvulsants may increase risk of adverse maternal and fetal health outcomes. While the increasing population use of these medications in the U.S. has been described, there is little information about whether their use has increased by women during pregnancy.

Objectives: To test the hypothesis that rates of antipsychotic and anticonvulsant medication use among pregnant women enrolled in Tennessee Medicaid increased from 1985 to 2005.

Methods: Tennessee birth and fetal death records were linked to Tennessee Medicaid data to conduct a retrospective cohort study of 296,817 women enrolled in Tennessee Medicaid throughout pregnancy who had a live birth or fetal death from 1985 to 2005. Filled prescriptions for medications of interest were considered to represent pregnancy exposures if the prescription was filled after the last menstrual period or the days supply for a prescription filled before pregnancy overlapped into pregnancy. The primary outcome measure was any use during pregnancy

of antipsychotics, anticonvulsants or lithium during pregnancy. Poisson regression was used to estimate trends over time.

Results: The adjusted rate of use of any study medication during pregnancy increased from 13.7 per 1,000 pregnancies to 44.6 per 1,000 pregnancies (adjusted rate ratio 3.2, 95% confidence interval 2.9–3.5) during the study time period. Use of atypical antipsychotics (21-fold increase) and anticonvulsant medications (sixfold increase) increased substantially. Prescribing of typical antipsychotics and lithium decreased. White, non-Hispanic, prima gravid, and older mothers were more likely to use almost every category of study medication.

Conclusions: There was a substantial increase in use of atypical antipsychotics and anticonvulsants among Tennessee Medicaid-insured pregnant women during the study period. Further examination of the maternal and fetal consequences of exposure to these medications during pregnancy is warranted.

804. Neonatal Outcomes Following Late Gestation SSRI Exposure

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Background: Prenatal SSRI exposure may increase the risk for adverse neonatal outcomes, but few studies have attempted to control for confounding due to underlying maternal psychiatric illness.

Objectives: To investigate neonatal outcomes following prenatal SSRI exposure during late gestation.

Methods: A retrospective cohort study was conducted using linked records from the Women's and Children's Health Network (WCHN) in South Australia. This included electronic data from the Women's and Children's Hospital (WCH) Perinatal Statistics Collection and the WCH Hospital Pharmacy Dispensing Records. Eligible women were those who gave birth to live singletons between September 2000 and December 2008 (n = 33,965). Main outcomes assessed were preterm birth, low birth weight, small-for-gestational age (SGA), neonatal hospitalisation and length of hospital admission. Statistical analyses were performed using a generalised linear model, yielding prevalence ratios (PRs) and 95% confidence intervals (CIs). Adjustments were made for sociodemographic, lifestyle and medical factors.

Results: Of eligible pregnant women, 221 received a dispensing for a SSRI (exposed), 1,566 did not receive a dispensing for any antidepressant but had a reported psychiatric illness (untreated psychiatric illness) and 32,004 did not receive a dispensing for any antidepressant and had no reported psychiatric illness (unexposed). Compared to women with an untreated psychiatric illness, infants of women with prenatal SSRI exposure had an increased risk of preterm birth (adjusted PR 2.13; 95% CI 1.61–2.82), low birth weight (aPR 2.04; 95% CI 1.27–3.26), admission to hospital (aPR 1.50; 95% CI 1.24–1.82) and length of hospital stay >3 days (aPR 1.82; 95% CI 1.10–3.02) but not SGA (aPR 1.10; 95% CI 0.70–1.72). Untreated psychiatric illness itself during pregnancy was associated with an increased likelihood of neonatal hospital admission (aPR 1.14; 95% CI 1.04–1.25), but not length of hospital stay >3 days (aPR 1.05; 95% CI 0.83–1.33).

Conclusions: These results add to the growing body of evidence of an association between prenatal SSRI exposure and a range of adverse neonatal outcomes even after controlling for untreated maternal psychiatric illness.

805. SSRI Use during Pregnancy and the Risk of Stillbirth and Neonatal Mortality

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Background: The Danish Medicines Agency recently issued a warning, concerning a possible association between in utero exposure to selective serotonin reuptake inhibitors (SSRI) and perinatal mortality. There are limited published studies addressing this issue.

Objectives: This study seeks therefore to investigate whether in utero exposure to SSRIs increases the risk of stillbirth or neonatal mortality.

Methods: Pregnancies were identified through the Danish Fertility Database. We calculated time of exposure to an SSRI using the Register of Medicinal Product Statistics. The risk of stillbirth or neonatal mortality associated with SSRI exposure was analyzed using multivariate logistic regression and propensity score matched models.

Results: We identified 920,620 pregnancies of which 12,425 were exposed to an SSRI. We did not find an association of stillbirth with exposure to SSRI during the first-trimester, adjusted odds ratio = 0.77 (95% CI 0.43–1.36), second-trimester, OR = 0.84 (95% CI 0.40–1.77), or third-trimester, OR = 1.06 (95% CI 0.71–1.58). We did not find an association of neonatal mortality with exposure to SSRI during the first-trimester, OR = 0.56 (95% CI 0.25–1.24), second-trimester, OR = 0.90 (95% CI 0.37–2.17), or third-trimester, OR = 1.27 (95% CI 0.82–1.99). Stratifying exposure to individual SSRIs revealed an association of third-trimester exposure to citalopram and neonatal mortality, OR = 2.49 (95% CI 1.33–4.65), which was rendered statistically insignificant after adjustment for multiple testing. Propensity score matched analyses revealed similar estimates.

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Conclusions: The present study shows no association between exposure to SSRIs during pregnancy and stillbirth or neonatal mortality. When stratifying to individual SSRIs we found a statistically significant association between third-trimester exposure to citalopram and neonatal mortality. Further studies are needed to corroborate these findings.

806. Antidepressant Use during Pregnancy and Risk for Preeclampsia in the US Medicaid Population

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Background: Previous studies suggest that women who use antidepressants during pregnancy have an increased risk for preeclampsia, yet the comparative safety of specific antidepressants remains unclear. Nationwide Medicaid Analytic eXtract (MAX) data has not previously been used to study drug safety during pregnancy.

Objectives: To evaluate the association between antidepressant classes and preeclampsia among pregnant women enrolled in Medicaid, the health insurance program for low-income individuals in the United States.

Methods: Within a previously identified cohort of 1,248,875 pregnancies from the 2000 to 2007 MAX, we used pharmacy dispensing records to identify gestational exposure to serotonin reuptake inhibitors (SSRI), serotonin-norepenephrine reuptake inhibitors (SNRI), tricyclics (TCA), or bupropion. Preeclampsia, severe preeclampsia, and depression were defined using ICD-9 codes. We identified 26,606 pregnancies in which women had both depression diagnoses and at least one antidepressant dispensing between gestational weeks 12–32 and 59,345 pregnancies in which women had depression and no antidepressant dispensings. We estimated relative risks (RR) for preeclampsia and 95% confidence intervals (CIs) with logistic regression and adjusted for delivery-year, age, race, parity, multifetal gestation, diabetes, disability, and number of depression diagnoses.

Results: Among women with depression and no antidepressant use, the risk for preeclampsia was 5.4%. Compared to this group, the RR for preeclampsia was 1.1 (CI: 1.0–1.2) for SSRIs, 1.8 (CI: 1.5–2.2) for SNRIs, 2.1 (CI: 1.5–2.8) for TCAs, and 1.2 (CI: 1.0–1.4) for bupropion as monotherapies. A similar pattern of associations was observed for severe preeclampsia. Compared to SSRIs, the RR for preeclampsia was 1.6 (1.3–2.0) for SNRIs and it was 1.9 (1.4–2.6) for TCAs.

Conclusions: SNRIs and TCAs were associated with a higher risk for preeclampsia than SSRIs. However, more detailed analyses are needed to assess the potential role of confounding. This study demonstrates that carefully identified pregnancy cohorts from nationwide Medicaid data can be used to study drug safety during pregnancy in this understudied population.

807. Use of Prescription Databases in Studies of SSRI Exposure in Pregnancy. Impact of Misclassification on Measured Risk Associations

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Background: Prescription databases are widely used in studies of drug safety in pregnancy, but noncompliance bias the results. Exposure to selective serotonin reuptake inhibitors (SSRI) recorded in prescription databases has, in a Nordic study, been shown to be a risk factor for persistent pulmonary hypertension of the newborn (PPHN)[1].

Objectives: To calculate the sensitivity and specificity of drug exposure recorded in the Norwegian Prescription Database (NorPD), to assess the impact of misclassification on the risk estimate in the Nordic study[1].

Methods: Design: Linkage of data from The Norwegian Mother and Child cohort study (MoBa) with drug exposure from NorPD. Data on dispensed SSRIs from NorPD for different time windows were extracted: early and late pregnancy (gestational day 1–55 and 140-birth) and early pregnancy with 30, 60 and 90 days prior to pregnancy. Self-reported drug use in early and late pregnancy in MoBa, was chosen as reference standard.

Setting: 27,656 women who participated in MoBa. *Outcome*: Odds ratio (OR) adjusted for misclassification of exposure. We assumed non differential misclassification in the assessment of bias[2].

Results: Sensitivity increased and specificity decreased when the time window in NorPD was expanded prior to pregnancy. Using the same time window as the Nordic study (+90 days prior to pregnancy), for use in early pregnancy, estimated sensitivity and specificity were 0.913 and 0.993. OR adjusted for misclassification, was 2.6, as compared to the unadjusted OR of 1.6 in the Nordic study. Adjusted OR for PPHN among users of SSRIs in late pregnancy was 2.7, compared with the unadjusted OR of 2.5.

Conclusions: Expansion of the time window in NorPD to include intervals prior to pregnancy led to lower specificity and higher degree of underestimation of the risk estimate in the Nordic study. After correction for misclassification the ORs for use in early and late pregnancy were almost similar. Specificity is a more powerful determinant of the

observed OR than is the sensitivity when the prevalence of exposure is low.

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808. Prevalence and Trends in the Use of Antipsychotics during Pregnancy in the U.S., 2001–2007

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Background: There is limited information on the prevalence of antipsychotic use during pregnancy.

Objectives: To estimate the prevalence of and temporal trends in antipsychotic use during pregnancy within a population-based cohort of pregnant women in the U.S.

Methods: We identified live born deliveries among women aged 15–45 years in 2001–2007 from 11 health plans participating in the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP). To be eligible, the women had to be continuously enrolled in the health plan with pharmacy benefits from 180 days before pregnancy through delivery. We ascertained prenatal exposure to antipsychotics from health plan pharmacy files, gestational age (based primarily on last menstrual period) from linked infant birth certificate files, and ICD-9-CM diagnosis codes from health plan claims data. We calculated the prevalence of prenatal antipsychotic use according to delivery year, trimester of pregnancy, and mental health diagnosis.

Results: Among 585,615 qualifying deliveries, 4,224 (0.72%) were to women who received an atypical antipsychotic any time from 60 days before pregnancy through delivery. The prevalence was highest during the first trimester at 0.52%, decreasing to 0.27% in the second trimester and 0.20% in the third trimester. Quetiapine was the most commonly used atypical antipsychotic (42% of atypical antipsychotic use), followed by olanzapine (32%) and risperidone (23%). Depression was the most common mental health diagnosis (63%) occurring in these women's records any time from 180 days before pregnancy through delivery, followed by bipolar disorder (43%) and schizophrenia (13%). Atypical antipsychotic use increased 2.5-fold during the study period, from 0.33% (95% CI: 0.29–0.37%) in 2001 to 0.82% (0.76–0.88%) in 2007. The use of typical antipsychotics remained stable at around 0.1% across the years studied.

Conclusions: The proportion of pregnancies exposed to atypical antipsychotics has increased 2.5-fold in recent years. Studies are needed to examine the comparative safety and effectiveness of these medications during pregnancy relative to other therapeutic options.

809. Does Maternal Lamotrigine Use Increase the Risk for Club Foot?

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Background: In an exploratory analysis of the EUROCAT Antiepileptic Database, we found an association between lamotrigine monotherapy and club foot without spina bifida (Dolk, 2008), based on five cases where 1.8 were expected ($p < 0.05$).

Objectives: To investigate whether there was independent evidence of an association between lamotrigine and club foot among subsequent registrations in the EUROCAT Antiepileptic Database, which would suggest that it was not a chance finding.

Methods: The study population of this independent dataset covered 1,272,600 births from 17 registries, born 2006–2009, including 31,718 malformed livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis. We calculated the proportion of club foot among non-chromosomal malformed pregnancy outcomes exposed to lamotrigine monotherapy (n = 26) and compared this with the proportion of club foot among non-chromosomal malformed registrations not exposed to any antiepileptic drugs (n = 26,686). We also compared this with the proportion of club foot among non-chromosomal malformed pregnancy outcomes exposed to other AEDs (n = 567) in the entire dataset (1995–2009, 5,125,510 births).

Results: We found four cases of club foot among 26 lamotrigine monotherapy exposed registrations instead of

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the expected 1.14 ($p < 0.05$) based on the non-exposed proportion of clubfoot of 4.4%. The proportion of club foot among pregnancy outcomes exposed to other AEDs was 4.1% in the entire dataset (old and new data). Of the total of nine club foot cases reported to date, eight were isolated and five were bilateral (one laterality unknown).

Conclusions: We examined the signal of an association between lamotrigine exposure in the first trimester of pregnancy and club foot in an independent dataset and found it again statistically significant. The significant association with club foot was specific for lamotrigine exposed, and not for other AEDs exposed. Club foot is a complex anomaly, related to various genetic and environmental factors. This indication should be interpreted with caution. We will continue to monitor with EUROCAT data and invite responses to this signal from existing cohort studies.

810. Use of Selective Serotonin-Reuptake Inhibitors during Pregnancy and the Risk of Clubfoot

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Background: Selective serotonin-reuptake inhibitors (SSRIs) are the most commonly prescribed anti-depressants. Previous studies have suggested that SSRIs may increase the risk of birth defects overall and one study found an elevated risk with clubfoot in an exploratory analysis.

Objectives: Using data from the Boston University Slone Epidemiology Center Clubfoot Study, we evaluated whether SSRI use increased the risk of clubfoot.

Methods: Mothers were interviewed within 1 year of delivery about sociodemographic factors, pregnancy events, and exposures. They were specifically asked if they experienced depression or anxiety or if they took any of the following SSRIs: Celexa (citalopram), Lexapro (escitalopram), Luvox (fluvoxamine), Paxil (paroxetine), Zoloft (sertraline) or Prozac (fluoxetine). Logistic regression models were used to calculate ORs and 95% confidence intervals (CIs).

Results: We included a total of 578 clubfoot cases and 2,032 non-malformed controls born between 2006 and 2011 in Massachusetts, New York, and North Carolina. Women who reported any SSRI use in the second through fourth lunar month of pregnancy (the relevant gestational period) were considered exposed. Reported SSRIs use was slightly higher in case mothers (4.8%) than control mothers (3.0%). The most commonly reported SSRI were sertraline and escitalopram, with cases reporting more use (2.1% and 1.4%) than control mothers (1.3% and 0.6%). After adjustment for maternal race and smoking, the OR for any SSRI use and clubfoot was 1.42 (95% CI: 0.9, 2.3). When individual SSRIs were examined, ORs were elevated for paroxetine and escitalopram, but numbers were small and confidence intervals were wide.

Conclusions: The observed OR for early pregnancy exposure to any SSRI is lower in magnitude than the previous report; drug specific risks varied widely (ORs 0.7–7.3), though numbers were too small to draw conclusions.

811. The Association between Sertraline, Fluoxetine, and Paroxetine and Major Birth Defects, Data from the National Birth Defects Prevention Study, 1997–2007

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Background: The association between selective serotonin reuptake inhibitors (SSRIs) and birth defects has been assessed in aggregate with conflicting results.

Objectives: We assessed the association between sertraline, fluoxetine and paroxetine and specific birth defects.

Methods: Data from the National Birth Defects Prevention Study (NBDPS) from 1997 to 2007 were used. Women who had an infant with a major birth defect (case-mothers) and a random sample of women who had liveborn infants without major birth defects (control-mothers) were interviewed, in English or Spanish, between 6 weeks and 2 years after the estimated date of delivery and were asked specifically if they took sertraline, fluoxetine or paroxetine. They were classified as exposed if they reported any use from 1 month before through the third month of pregnancy. Logistic regression was used to estimate odds ratios (aOR) and 95% confidence intervals (CI) adjusted for maternal race/ethnicity, education, pre-pregnancy obesity and smoking for 88 medication-birth defect combinations that had at least three exposed cases.

Results: Sertraline, fluoxetine and paroxetine were used by 89 (1.1%), 62 (0.8%) and 37 (0.5%) of the 8,115 controls respectively. There were no defects associated with all three SSRIs. For sertraline, increased odds ratios were observed for glaucoma/anterior chamber defects (aOR = 3.4, 95% CI 1.4–8.6) and pulmonary valve stenosis (aOR = 2.0, 95% CI 1.3–3.2). Fluoxetine was associated with Dandy Walker malformation (aOR = 3.71, 95% CI 1.1–12.1), aortic stenosis (2.4, 95% CI 1.1–5.7), esophageal atresia (2.3, 95% CI 1.1–4.7) and craniosynostosis (2.0, 95% CI 1.1–3.5). Paroxetine was associated with anencephaly (2.7, 95% CI 1.0–6.8), total anomalous pulmonary venous return (4.2, 95% CI 1.5–11.8), omphalocele (3.5, 95% CI 1.4–9.1) and gastroschisis (2.1, 95% CI 1.0–4.4).

Conclusions: Sertraline, fluoxetine and paroxetine were each associated with some specific birth defects, but without any common pattern. Some of the associations observed are likely due to chance and confirmation by additional research is needed.

812. Pregnancy Outcomes in Women Exposed to Adalimumab for the Treatment of Rheumatoid Arthritis

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Background: The fully human, anti-tumor necrosis factor monoclonal antibody adalimumab (ADA) is approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease and psoriasis in the United States and elsewhere. The effect of ADA during human pregnancy is unknown.

Objectives: This preliminary description of outcome data collected by the Organization of Teratology Information Specialists (OTIS) provides some information on the safety of ADA when used by pregnant patients with RA.

Methods: In this ongoing, prospective cohort study, women who reside in the U.S. or Canada and have been treated with ADA for RA during the first trimester of pregnancy are enrolled during pregnancy, followed for 1-year postpartum, and medical records are obtained. Additionally, all live born infants receive a dysmorphology exam for both major and minor structural anomalies. Outcomes are compared with a disease-matched comparison group of women without ADA exposure, and a comparison group of pregnant women who neither have an autoimmune disease nor have been treated with ADA, followed in the same manner.

Results: Between November 2004 and January 2012, pregnancy outcomes have been collected on 297 women in the ADA RA cohort study. Of these, 66 are enrolled in the ADA-exposed cohort, 71 in the disease-matched comparison group, and 160 in the healthy comparison group. Major birth defects were reported in 5.4% of the healthy comparison pregnancies, in 3.1% of the ADA-exposed RA group, and in 4.4% of women in the RA disease-matched (non-ADA-treated) group. Furthermore, there was no evidence of a pattern of either major or minor structural defects in the ADA-exposed group.

Conclusions: Based on preliminary data, there is no evidence of an association between ADA exposure in pregnant women with RA and a specific pattern of major or minor malformations.

813. Caffeine Intake during Pregnancy and the Risk of Preterm Birth

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Background: Given that pregnant women commonly consume caffeinated beverages, caffeine intake during pregnancy has been the subject of many epidemiological studies regarding its potential reproductive adverse effects on the foetus. The risk for preterm birth is one of the most studied outcomes in animal studies.

Objectives: To quantify the association between caffeine intake during pregnancy and the risk of preterm birth.

Methods: A questionnaire was mailed to 8,505 women randomly selected from the Quebec Pregnancy Registry which was created with the linkage of three administrative databases: RAMQ, MED-ECHO, and ISQ. Eligible women gave birth to a singleton liveborn between January 1998 and December 2003 in Quebec and were insured by the RAMQ drug plan for at least 12 months before and during pregnancy. Questionnaire data were linked to the Registry data and responders constituted the study population. Prematurity was defined as a delivery occurring before 37 weeks of gestation; the remaining was defined as term pregnancy. Descriptive statistics and multivariate logistic regression models were used to analyze data.

Results: Of the 3354 (40.6%) responded to the questionnaire. In order to have a representative sample of the registry, only 7% of birth defects cases were selected. Given that, our present study included 1648 pregnancies. Among them 506 (30.7%) cases of prematurity were identified. Adjusting for potential confounders, caffeine intake during pregnancy was not associated with the risk of prematurity (OR = 0.96, 95% CI [0.72–1.28]).

Conclusions: Caffeine intake during pregnancy does not significantly increase the risk of prematurity.

814. Predictors of Caffeine Intake during Pregnancy

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Background: Despite governmental recommendations to pregnant women on the reduction of caffeine intake, many recent studies report that a considerable proportion of them maintain this consumption during their pregnancy.

Objectives: To quantify the prevalence and identify the predictors of caffeine intake during pregnancy.

Methods: A questionnaire was mailed to 8,505 women selected from the Quebec Pregnancy Registry. This Registry was created with the linkage of three administrative and hospital databases: Regie de l'assurance maladie du Quebec (RAMQ), Med-Echo, and l'Institut de la statistique du Quebec (ISQ). Eligible women were continuously insured by the RAMQ drug plan for at least 12 months before and during pregnancy, and gave birth to a live born infant between January 1998 and December 2003 in Quebec. Questionnaire data were linked to the Registry data

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and responders constituted the study population. Descriptive statistics and multivariate logistic regression models were performed.

Results: Among the 3,345 women (39.4%) who answered the questionnaire, 2,877 (87.3%) consumed caffeine before pregnancy and 2,299 (71.8%) continued their consumption during pregnancy. Maternal age, place of birth (rural/urban), medication insurance status, maternal hypertension, hospitalisation and smoking before pregnancy were all increasing the likelihood of caffeine intake during pregnancy; higher education level and illicit drug use were decreasing the likelihood of caffeine intake during gestation.

Conclusions: Caffeine intake is common during pregnancy. Given that the risk of caffeine use during gestation remains controversial, predictors identified in this study will help physicians identify women that could potentially be at risk.

815. Prenatal Care and Antiretroviral Therapy Use during Pregnancy among HIV- Infected Women on Medicaid

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Background: The use of antiretroviral therapy (ART) during pregnancy is considered the standard of care for HIV-infected (HIV+) pregnant women. In poor populations, delayed prenatal care may hinder appropriate ART treatment during pregnancy.

Objectives: To characterize prenatal care and ART use in HIV-infected pregnant women enrolled in Medicaid.

Methods: We linked data from Tennessee Medicaid files and vital records to evaluate pregnancies among HIV+ females delivering between 1994 and 2009. HIV status and pregnancy outcomes were identified from Medicaid claims and birth certificate files.

Results: Seven hundred and ninety-one deliveries among HIV+ females were included (including 23 twin births). At delivery, the women had mean age of 26, 83% were Black, 86% had <13 years of education, and 12% had mental health disorders. Of 17% were not prescribed ART during pregnancy; among those with a prescription, 33% had their first ART prescription in the first trimester, 45% in the second and 22% in the third. Prenatal care was initiated in the 1st trimester for 56%, 2nd trimester for 31%, and 3rd trimester for 7% of women, while 6% had no prenatal care. Late (third trimester) or absent prenatal care was more common in women without ART prescriptions during pregnancy (33%) than in those with them (9%). Absent or late access to prenatal care remained stable over the study period.

Conclusions: An important obstacle for appropriate HIV treatment during pregnancy in this underserved population may be delayed prenatal care, suggesting greater prioritization of obstetric/gynecologic services in Medicaid recipients of childbearing age.

816. Trends in Dispensations of High Dose Folic Acid and Birth Prevalence of Major Congenital Malformations

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Background: Recent evidence suggests that periconceptional folic acid supplementation could not only prevent neural tube defects but also other major congenital malformations (MCM) such as cardiac, limb and urogenital defects. In Canada, high dose of folic acid (5 mg) is recommended for women with higher risk for neural tube defects. In the Province of Quebec, low dose folic acid is widely available over the counter but high dose requires a physicians' prescription and is therefore reimbursed by the public drug plan.

Objectives: To assess trends in dispensations of high dose folic acid and birth prevalence of major congenital malformations.

Methods: We used the Quebec Pregnancy Registry to analyse trends in periconceptional use of high dose folic acid and for birth prevalence of major congenital malformations, for the 10-year period comprised between January 1998 and December 2008. Folic acid use was defined as having dispensations of folic acid for 30 days before the first day of gestation and 70 days after, and at least one dispensation was overlapping the first day of gestation. Annual trends were analyzed using the Cochran-Armitage test.

Results: We identified 152,392 pregnancies and babies. The annual prevalence of periconceptional folic acid use increased from 0.17% to 0.80% ($p < 0.05$) during the study period; birth prevalence of major congenital malformations increased from 750.7 to 1156.6 cases per 10,000 live births, $p < 0.05$). More specifically, 3.70 times more women were using periconceptional high dose folic acid and this was associated with 42% increase in the prevalence of cardiac malformation, 8% increase in neural tube defect and 75% increase in urogenital defects.

Conclusions: Although there was an increase in the use of periconceptional folic acid over the past 10 years, there was no decrease in the prevalence of major congenital malformations. The observed increasing trend in the prevalence of MCM can partly be explained by the use of more sensitive diagnostic tools as well as the increasing maternal age at delivery observed in the last decade.

817. Antihistamines Use in Early Pregnancy and Risk of Birth Defects

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Background: Several studies have reported an association between use of specific antihistamines (AH) in early pregnancy and certain specific birth defects, e.g., loratadine and hypospadias, or diphenhydramine and oral clefts.

Objectives: To test 16 previously hypothesized associations between specific AH and specific birth defects.

Methods: We used data ascertained from 1997 to 2009 as part of the Slone Epidemiology Center Birth Defects Study (BDS). Mothers were interviewed within 6 months of delivery about a wide range of factors, including details of medications (Rx and OTC) use. We studied prenatal exposure to specific AH among 13,213 infants with malformations and 6,982 non-malformed controls. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for specific malformations associated with 1st trimester exposure to AH compared to nonuse during pregnancy, stratifying by pregnancy year and study region and adjusting for potential confounders, including indication for use.

Results: Overall, 11.4% of cases and 10.4% of controls were exposed to AH during the 1st trimester. The most common AH were diphenhydramine (4.2%), loratidine (3.1%), doxylamine (1.9%), and chlorpheniramine (1.7%). Where estimates were stable, none supported the previously-hypothesized associations. In exploratory analyses involving multiple comparisons, 5 had elevated ORs with lower 95% CI bounds exceeding 1.0: diphenhydramine and D-transposition of great arteries (OR: 2.3, 1.1–5.0); doxylamine and cystic kidney disease (OR: 2.7, 1.3–5.6); and chlorpheniramine and neural tube defects (OR: 2.6, 1.1–6.1), hypoplastic left heart syndrome (OR: 4.9, 1.6–14.9), and great veins defects (OR: 3.3, 1.1–10.0). One comparison, loratadine and oral clefts, had an OR of 0.5 (0.3–0.9).

Conclusions: Our findings do not provide any meaningful support for previously-posited associations; meanwhile, we identified associations that had not been previously suggested. We suspect that many if not all previous associations were probably chance findings in the context of multiple comparisons, a situation which may also apply to our new findings from the BDS.

818. Exposure to NSAIDs during Pregnancy and Risk of Development of Birth Defects: A 4 Months Study in a Large Indian Hospital

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Background: NSAIDs are the most common drugs prescribed to pregnant women and may have adverse effects that are commonly overlooked, they are important to study, as they may cause congenital abnormalities or miscarriages. The use of NSAIDs may cause an increased risk of miscarriage if used around the time of conception.

Objectives: To determine the extent of NSAID exposure during pregnancy, the adverse events associated with its use and the risk of development of any birth defects.

Methods: The study was conducted in one of the large hospital in India from October 2011 to January 2012. All pregnant women attending the out patients clinic and those admitted as in patients, prescribed NSAIDs were included. The medical records were then scrutinized to determine the extent of adverse events reported.

Results: A total of 5,515 pregnant women were prescribed various NSAIDs during this study. The most common NSAID prescribed was paracetamol (5,319; 96.4%), followed by diclofenac (173; 3.1%) and aspirin (23; 0.4%). The commonest indication for prescribing paracetamol was pain and fever during all trimesters of pregnancy; diclofenac (1st 2nd trimester of pregnancy) for severe pain and aspirin (1st and 2nd trimerster) for recurrent abortion; hypertension. The most common adverse event reported with the use of paracetamol was nausea dry mouth (139; 2.6%); dizziness (31; 0.6%), allergic reactions (11; 0.2%); yellowing of skin (3; 0.05%) and hypertension (2; 0.05%). With diclofenac use the commonest adverse events reported was severe GI disturbances and hypertension and with aspirin use, gastric irritation.

Conclusions: No congenital abnormalities were detected in our study. Physicians are indeed very careful in India to prescribe medications and pregnant women also tend to avoid taking any medication during pregnancy unless there is increased need. Routinely pregnant women should be monitored for any drug use during pregnancy and any congenital abnormality detected in newborns should be reported.

819. Abstract Withdrawn by Author.

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820. Prescription of Drugs during Pregnancy in Japan

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Background: A number of studies demonstrated that prescription drugs were commonly used during pregnancy. However, information on prescription of drugs during pregnancy in Japan was not available.

Objectives: To provide information on the prevalence of prescription of drugs during pregnancy and the classes of drugs prescribed to pregnant women in Japan

Methods: A retrospective study was conducted with Japanese medical claim data from January 2005 to June 2011. Female members who delivered an infant between December 2005 and June 2011 and who were enrolled continuously with prescription drug coverage for at least 11 months before the date of delivery were identified. Female who did not have an available data on the gestational age were excluded. Period of pregnancy was defined by the data on gestational age and divided into three trimesters (first trimester, 0–15 gestational weeks; second trimester, 16–27 gestational weeks; third trimester, 28 gestational weeks or more).

Results: During study period, 19,282 women (mean age; 30.5 ± 4.7 years) were met the inclusion criteria for this study. Ninety-eight percent of women (n = 18,971) were prescribed at least one drug during pregnancy. The prevalence of women who were prescribed at least one drug was 58.2% (n = 11,216), 55.4% (n = 10,676), and 87.3% (n = 16,826) during first trimester, second trimester, and third trimester, respectively. Haematinics, iron and all combinations was most frequently prescribed drug class (70.2%, n = 13,527) during pregnancy. The most frequently prescribed drug class was plain antispasmodics and anticholinergics (11.6%, n = 2235), labor inhibitors (15.8%, n = 3043), and haematinics, iron and all combinations (51.7%, n = 9971) during first trimester, second trimester, and third trimester, respectively.

Conclusions: We found that prescription of drugs during pregnancy was common in Japan.

821. Infant Outcomes among Pregnant Women Who Used Oseltamivir for Treatment of Influenza during the H1N1 Epidemic

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Background: In March 2009, a novel H1N1 influenza A virus was identified in Mexico and spreaded rapidly across many countries. Pregnant women are at increased risk for hospital admission, death, and adverse fetal outcomes associated with influenza pandemic. The efficacy and safety of oseltamivir in children aged ≥1 year and in adults has been well established, and it has been used extensively for the treatment and prevention of 2009 H1N1 influenza. The benefit of treatment of pregnant women with antiviral medications is presumed to outweigh its risk.

Objectives: To examine the association between maternal oseltamivir treatment for influenza and infant outcomes.

Methods: This was a retrospective cohort study using a population-based maternal newborn database including women who gave birth to a singleton infant in the Canadian province of Ontario between November 2009 and April 2010. Risks of small for gestational age (SGA, 10th percentile), severe SGA (3rd percentile), preterm birth (< 37 weeks of gestation), very preterm birth (< 32 weeks of gestation), and 5-minute Apgar score < 7 as associated with maternal exposure to oseltamivir were analyzed by multivariate regression.

Results: A total of 55,355 women with a singleton birth were included in this study. Among them, 1,237 (2.2%) women received oseltamivir for treatment or prevention of influenza during pregnancy. Women who took oseltamivir during pregnancy were less likely to have an SGA infant based on the 10th percentile for growth (aRR 0.77; 95% CI 0.60–0.98). No association between maternal use of oseltamivir with severe SGA, preterm birth, very preterm birth or low Apgar score was observed.

Conclusions: We found no evidence of an association between maternal use of oseltamivir for influenza and adverse newborn outcomes.

822. Online Purchasing of Isotretinoin: E-Pharmacies Provision of Safety Information

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Background: The purpose of Isotretinoin Pregnancy Prevention Programs (PPP) is to utilise a variety of approaches and strategies to control the prescription of, and diminish the risks of women of child bearing age receiving this medication during pregnancy. With the growing phenomenon of online pharmacies, consumers are now able to purchase Isotretinoin online without the requisite safety procedures.

Objectives: A structured survey of e-pharmacies selling Isotretinoin to evaluate what safety measures and regulations are in place for women of child bearing age.

Methods: The terms "buy" and "Isotretinoin" was entered into five commonly used search engines. Ten different online pharmacies URL's (Uniform Resource Locator) from each search engine, all selling isotretinoin, were stored for evaluation. The safety information content of each of the 50 sites was evaluated independently for accuracy and completeness by two raters using criteria derived from the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare Regulatory Agency (MHRA) for dispensing Isotretinoin to women at risk of pregnancy.

Results: Eight (16%) of the websites made no reference to the use of Isotretinoin in pregnancy. Information provided by 35 (70%) of the websites was of poor or very poor quality in relation to the need for and recommended methods for pregnancy prevention. Misleading statements were recorded on several of the websites. Isotretinoin could be readily purchased from 42 (84%) of the sites without a valid prescription.

Conclusions: Women of child bearing age have the option to self-purchase Isotretinoin directly from web sites that do not provide any form of risk assessment, pregnancy prevention education, or warnings of the dangers associated with taking this medication. These findings have implications for the design of Pregnancy Prevention Programmes, for clinicians, and for legal regulation of internet pharmacies.

823. Asthma Management in Pregnancy

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Background: Asthma is common in pregnancy, however, research is limited regarding the extent and timing of changes in asthma management associated with pregnancy.

Objectives: To identify changes in treatment level and asthma exacerbation rates associated with pregnancy, whilst controlling for seasonal influences.

Methods: Pregnant women with diagnosed and currently treated asthma were identified from the UK General Practice Research Database between 2000 and 2008. For each woman, all asthma medicine prescribing during the study period was identified. For short-acting H_2-agonists (SABAs), no duration of treatment was estimated. However for all other products, duration of treatment was estimated based on amount and dosage prescribed. For each product combination the British Thoracic Society medication-defined asthma treatment step was identified, where possible. Asthma exacerbations (evident from medical codes combined with short-course oral corticosteroids or hospitalisations) were identified during pregnancy and in the corresponding previous 12 months, to control for seasonality. Analyses of changes in asthma treatment and exacerbation rates during pregnancy relative to the previous 12 months were stratified by trimester and by asthma activity level.

Results: From 14,141 pregnancies in 12,828 women, 68% received prescriptions for SABAs only and 41% for inhaled corticosteroid (ICS) containing medication; 77% were managed with asthma treatment Step 1 or 2. Low persistence of ICS use, defined as a gap of up to 60 days between prescriptions, was common: 75% of those experiencing a step down in treatment returned to their previous medication within a 2-month period. In 45% of pregnancies an increase in average treatment step was observed, whereas in 26% the treatment step decreased, and treatment intensity remained the same in 30% of pregnancies. Acute exacerbations occurred in 5% of pregnancies compared to 6% in the same season 1 year prior to the pregnancy ($p < 0.001$).

Conclusions: An increase in average asthma treatment step was observed in almost half of pregnant women in this study, with a significant reduction in season-specific exacerbations. These results highlight the need for careful asthma management during pregnancy.

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824. Is the Use of Asthma Medication in Pregnancy in Accordance with Guidelines?

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Background: Adequate control of asthma during pregnancy is of great importance for the well-being of both mother and baby. In spite of this, research shows that many women are concerned about the risks of their asthma-medication for their unborn child and would consider discontinuation[1].

Objectives: We determined the prescription of asthma-medication around pregnancy to investigate the continuation of the use of the different asthma medications during pregnancy in relation to current guidelines.

Methods: This study was performed using the pregnancy database that is part of the population based pharmacy prescription interaction database (IADB). We included 25,709 pregnancies with data from 1994 to 2009, of which complete data of prescription drugs were available during the study period from 1 year before the theoretical pregnancy-period of 273 days, until 6 months after birth. We selected all pregnancies where the mother had at least one prescription of asthma medication during the study period. For these pregnancies, we identified all prescriptions of asthma medication and oral corticosteroids.

Results: Of the 2072 (8.1%) pregnancies had at least one prescription of asthma medication during the whole study period. There is a significant decline ($p = 0.008$) in prescriptions for asthma-medication in the first trimester of pregnancy compared to the trimester before pregnancy, from 2.94% to 2.56%, especially for the prescription of long-acting bronchodilators with a decline in prescription rate from 0.63% to 0.36% ($p < 0.001$). Although most asthma medication is continued throughout pregnancy, 29.8% of women with at least three prescriptions of controller medication in the year before pregnancy stopped their controller therapy when getting pregnant.

Conclusions: Guidelines stress the importance of maintaining adequate asthma control during pregnancy. Still many women stop their controller therapy when they get pregnant, especially preparations containing a long-acting bronchodilator. The treatment of pregnant asthmatic women can be improved, leading to better health for mother and child.

Reference 1 Chambers K: Asthma education and outcomes for women of childbearing age. *Case Manager* 2003; 14: 58–61.

825. The 2009 Influenza Pandemic, Vaccination during Pregnancy and Fetal Death: A National Registry-Based Study in Norway

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Background: Studies have indicated an increased occurrence of miscarriages after influenza infections during pregnancy. During the influenza A(H1N1)pdm09 pandemic, pregnant women were recommended influenza vaccination. Reports of miscarriages after vaccination raised concerns about the safety of vaccination with adjuvanted influenza vaccines during pregnancy.

Objectives: The aims of the current study was to estimate the risk of fetal death after being pregnant during the influenza pandemic, after influenza vaccination in pregnancy and after receiving a doctor's diagnosis of influenza during the main pandemic wave.

Methods: National registers and primary care reimbursement data were linked to provide vaccination status, birth records, diagnosis of influenza infection and background information all women in Norway between 13 and 49 years of age. Cox regression models with gestational day as the time metric, fetal death as outcome, and vaccination status, influenza diagnosis and pregnancy during the main pandemic wave as time-dependent variables, provided hazard ratios (HRs) for fetal death following vaccination with an adjuvanted pandemic influenza vaccine and exposure to influenza in pregnancy.

Results: Of 1,153,738 women aged 13–49 living in Norway in 2009, 117,026 had birth records from 2009 or 2010. There were 537 fetal deaths. Of 42,817 women who were in the second or third trimester during the main pandemic wave, 54% were vaccinated. Women who were pregnant during the main pandemic wave and women who were registered with a doctor diagnosis of influenza in pregnancy during the main pandemic wave had a statistical significant increased risk of fetal death. Vaccination during pregnancy was not associated with an increased risk of fetal death.

Conclusions: There was an increased risk of fetal death in women who were pregnant during the major wave of the pandemic influenza, and in women receiving a doctor diagnose of influenza during the main pandemic wave. Vaccination in pregnancy was not associated with an increased risk of fetal death.

826. Outcomes of Infants Born to Pregnant Women Who Received Influenza A (H1N1) 2009 Live Attenuated Monovalent Vaccine: Enhanced Surveillance Using the Vaccine Adverse Event Reporting System (VAERS)

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Background: Pregnant women were a priority group for influenza inactivated A (H1N1) 2009 monovalent vaccine; live-H1N1 vaccine was not recommended during pregnancy.

Objectives: To characterize infant outcomes for pregnant women who received live-H1N1 vaccine and were reported to the Vaccine Adverse Event Reporting System (VAERS).

Methods: We reviewed all US VAERS reports of pregnant women who received live-H1N1 vaccine without a reported associated adverse event (AE) during 10/09-06/10 We requested and reviewed delivery and infant medical records during the first 6 months after birth.

Results: We identified 113 VAERS reports that stated live-H1N1 vaccine had been received during pregnancy and no AE was reported. We obtained follow-up maternal records on 95 (84%) reports (34% were vaccinated in the first trimester). Reports included: 10 (10.5%) spontaneous abortions, one elective abortion, and 86 live births (one twin). No maternal deaths occurred. Three premature deliveries occurred at 35–36 weeks. Seven neonates/infants had temporary serious conditions: presumed sepsis and respiratory distress (2), vesicular skin lesions (1), urinary tract infection (1), prematurity with low birth weight (1), hyperbilirubinemia (1), and RSV bronchiolitis with otitis media. Three (3.5%) infants had ≥1 congenital anomalies noted at birth: one cleft palate, one cleft lip (with patent foramen ovale, patent ductus arterious), and one microtia. Follow-up records were available for 67/86 (78%) infants. One infant death occurred in a 2.5 month-old male due to pertussis. No other clinically important conditions were identified in infants.

Conclusions: Rates of spontaneous abortion, pre-term birth and overall birth defects in pregnant women vaccinated with live-H1N1 were similar or lower to published background rates. In addition, no concerning pattern in birth defects or medical conditions in infants was identified.

827. Influenza A(H1N1)pdm09 Vaccination in Pregnancy and Risk of Fetal Death

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Background: The 2009 pandemic influenza A(H1N1) vaccination campaigns targeted pregnant women but limited information is available on the fetal safety of H1N1 vaccination in pregnancy.

Objectives: This study aimed to investigate whether vaccination in pregnancy with an adjuvanted influenza A(H1N1)pdm09 vaccine was associated with increased risk of fetal death.

Methods: We conducted a nationwide register-based cohort study in Denmark including all clinically recognised singleton pregnancies that ended between November 2009 and September 2010. Individual-level data on exposure to an inactivated AS03-adjuvanted influenza A(H1N1)pdm09 vaccine (Pandemrix) and potential confounders were linked to the study cohort using a unique person identifier. Cox regression was used to estimate hazard ratios (HR) of fetal death comparing H1N1 vaccinated and unvaccinated pregnancies, adjusting for propensity scores. The primary outcome was fetal death (spontaneous abortion and stillbirth combined); the secondary outcomes were spontaneous abortion (defined as occurring between the start of week 7 and the end of week 22 of gestation) and stillbirth (defined as delivery of a dead fetus after 22 completed weeks of gestation) analysed separately.

Results: The cohort comprised 54,585 pregnancies; 7,062 (12.9%) were vaccinated against influenza A(H1N1)pdm09 during pregnancy. Overall, there were 1,818 cases of fetal death (1,679 spontaneous abortions and 139 stillbirths). Exposure to the influenza A(H1N1)pdm09 vaccine was not associated with increased risk of the primary outcome of fetal death (adjusted HR 0.79, 95% CI 0.53–1.16), or the secondary outcomes of spontaneous abortion (adjusted HR 1.11, 95% CI 0.71–1.73) and stillbirth (adjusted HR 0.44, 95% CI 0.20–0.94). Estimates for fetal death were similar in pregnant women with (adjusted HR 0.82, 95% CI 0.44–1.53) and without comorbidities (adjusted HR 0.77, 95% CI 0.47–1.25).

Conclusions: This large cohort study found no evidence of increased risk of fetal death associated with exposure to an adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy.

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828. Outcomes of Drug Use during Pregnancy: A Novel Database in the Netherlands To Study Drugs Risk on the yet Unborn

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Background: Insight into comorbidities and detailed drug exposure before and during pregnancies as well as outcomes in children is pivotal to perform pharmacoepidemiological pregnancy outcome studies.

Objectives: To construct a database that captures both detailed drug exposure before and during pregnancy as well as pregnancy related information and outcomes of the neonate (and other relevant clinical information) by linking the Netherlands Perinatal Registry (PRN) with the PHARMO Record Linkage System (RLS).

Methods: The PRN is an anonymous nationwide registry, including data from the midwifery, the obstetrics and the neonatology/pediatrics registry. The PHARMO RLS includes data from multiple healthcare databases such as drug dispensings, hospitalizations, GP data and clinical laboratory measurements and covers approximately 20% of the Dutch population. Both databases were linked using different record linkage techniques. Key variables (e.g., maternal age, gestational duration, parity, singleton birth) were assessed to determine comparability between the PRN and the linked PRN-PHARMO RLS pregnancies.

Results: The linkage of 1,453,504 pregnancies registered between 2000 and 2007 in the PRN with PHARMO RLS resulted in a cohort of 151,250 women with complete drug and clinical data available for 203,972 pregnancies. Linked pregnancies were comparable with all pregnancies. In 67% of all pregnancies at least one prescription drug was used. The most frequent used drugs included anti-anemic preparations (26%), antibacterials (20%) and gynecologic anti-infectives (14%). As dispensing date, duration and dose is recorded in the PHARMO RLS, exposure per trimester can be assessed and related to birth outcomes, such as prematurity and congenital defects as recorded in the PRN.

Conclusions: Linkage of the Netherlands Perinatal Registry and the PHARMO RLS creates the possibility to study detailed drug utilization and comorbidities of mothers before, during and after pregnancy and of children which enables to study potential adverse effects that might impact pregnancies or child development later in life.

829. Epidemiology of Major Congenital Malformations with Specific Focus on Teratogens

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Background: Major congenital malformations (MCM) are significant causes of infant morbidity and mortality and constitute important societal and economic burden.

Objectives: Specific objectives were to: (1) summarize internationally reported prevalence of MCMs based on registries and surveillance systems; (2) describe the epidemiology of different MCM types including critical periods, causative factors; (3) to identify the role played by principal known teratogens on the increase in the risk of MCM; and (4) determine challenges associated with the epidemiologic assessment of potential risk factors for MCMs as well as potential preventive measures.

Methods: We conducted a literature review to synthesize current evidence on MCM.

Results: It is estimated that 7.9 million infants worldwide are born every year with a MCM, yet there is considerable variation in reported rates across countries. This may be attributable to varying definitions arising from heterogeneity among different classes with respect to critical periods for embryogenesis and organogenesis. There is also substantial etiologic heterogeneity among MCM classes that potentially contribute to challenges in epidemiologic studies. Modifiable factors such as pharmacologic exposures have received considerable attention and a number of drugs have been shown to be teratogenic including folic acid antagonists, angiotensin converting enzyme inhibitors, antidepressants, anticonvulsants, coumarin derivatives and retinoids including isotretinoin.

Conclusions: The majority of MCM are due to unexplained causes; other contributing factors include genetics, multifactorial inheritance, environmental factors, maternal-related conditions, and maternal drug or chemical exposure. However, there remains a need to better understand the epidemiology of MCM when studying drug effect during gestation.

830. Time Trends and Risk Factors for Medication Use during Pregnancy

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Background: In assessing the risk benefit of drug use during pregnancy it is important to evaluate not only the relative safety of specific drugs but also the extent of their use. To date, only few descriptive studies have addressed the subject of trends in drug use during pregnancy.

Objectives: To analyze trends of drug use among pregnant women according to ethnic group, and to evaluate the adjusted risk factors associated with metoclopramide, PPIs and H_2 blockers in these populations.

Methods: A population based retrospective cohort including 100,914 pregnant women giving birth in Soroka medical center between the years 1999–2009, was conducted. A time trend analysis was preformed for consumption of various drug groups and compared by ethnic groups (Jews vs. Bedouins). Risk factors associated with use of metoclopramide, PPIs or H_2 blockers were assessed by multivariate logistic regression models controlling for: maternal age, ethnicity, parity, year of birth, GDM, prior diabetes mellitus, smoking, lack of prenatal care, gender, primigravidity and duration of the pregnancy.

Results: The percentage of women using any drug during pregnancy in our cohort was similar to other developed countries. The trend of drug use during pregnancy was not stationary and revealed opposite trends for different drug groups. Furthermore the nature and direction of the trends differed by ethnicity. The overall use of drugs and of prescription drugs was higher among Jewish vs. Bedouins women, though this difference appeared to be closing. In contrast, use of metoclopramide, PPIs or H_2 blockers was significantly higher in Bedouin than in Jewish women. There was a 48-fold increase in PPIs use by Bedouin women from 1999 to 2009, (adj OR for use by Bedouin was 2.53, 95% CI = 2.26–2.84, as compared to Jewish). This discrepancy grew each year. Also, we found a steep rise in consumption of folic acid.

Conclusions: This study found differences in trends of drug use and risk factors by ethnicity. Further qualitative and quantitative research is needed to evaluate the effects of socioeconomic variables on drug use and assess whether the disparity found stems from differences in health services.

831. Analysis Using of Drugs during Pregnancy in the Clinical Centre University of Sarajevo (CCUS) for Year 2011

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Background: Drugs in pregnancy should only be taken or used when essential, thereby avoiding many unnecessary and unknown risks. The physician should make a proper decision when choosing the drug, on the benefits and risks for the mother to the fetus.

Objectives: Examine the characteristics of pregnant women, gestational age at which drugs were applied, the type of medication and recommendations of clinical pharmacologist.

Methods: Descriptive and retrospective study. We analyzed data of pregnant women by age, gestational age of exposure to drugs and drug types. We used data from our registry of pregnant women, who addressed at Department of Clinical Pharmacology CCUS during year 2011.

Results: From a total of 83 pregnant women examined, 65 were taking one or more drugs; in average of two and maximum of nine. The average age of women was 30 years (max 40, min 21). The most of women (n = 61, 74%) used medications in the first trimester of pregnancy. Some of women (n = 18, 30%) took drugs in the period all or nothing. Two pregnant women were taking medication (2%) during the second trimester, and two prior of conception. In this study pregnant women used mostly antibiotics (beta lactams), pain killers (ibuprofen, diclofenac and metamizol) and antipsychotics.

Conclusions: Although pregnant women were taking medication during organogenesis, they used relatively safe medications for a short time. The exception is the metamizol on which there is insufficient data on adverse effects on the fetus. We recommended that all pregnant women regularly inspected by gynecologists.

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832. Maternal Medication and Herbal Use and Risk of Hypospadias: Data from the National Birth Defects Prevention Study, 1997–2007

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Background: Maternal use of some medications during pregnancy has been associated with risk of hypospadias, a birth defect in male offspring.

Objectives: To investigate associations between maternal use of selected medications during early pregnancy and the risk of hypospadias.

Methods: We used data from the National Birth Defects Prevention Study, a multi-site, population-based, case–control study. We analyzed data from 1,537 case infants with second or third degree isolated hypospadias and 4,314 male control infants born from 1997 to 2007. Exposure was based on reported use of any prescription or over-the-counter medication or herbal product. We analyzed components of these products for which there were at least five exposed cases, from 1 month before to 4 months after conception, excluding topicals, vitamins, minerals, and products for which the components were unknown. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using multivariable logistic regression adjusting for maternal age, race/ethnicity, education, pre-pregnancy body mass index (BMI), parity, maternal sub-fertility, study site, and year of due date in 2 years increments.

Results: Of the 195 medication components with at least five exposed cases, 89 components met the inclusion criteria and were assessed – 28 herbal and 61 non-herbal components. Hypospadias was associated with reported use of cephalexin (aOR 3.06; 95% CI 1.02, 9.18), phenylpropanolamine HCl (aOR 2.68; 95% CI 1.06, 6.80), and ibuprofen (aOR 1.16; 95% CI 1.00, 1.34). Results for all other components were null.

Conclusions: We replicated a previously observed association between maternal exposure to phenylpropanolamine HCl and hypospadias. The associations with cephalexin and ibuprofen have not previously been reported. Given the exploratory nature of the analyses, these results should be considered hypothesis-generating. Better understanding of the potential fetal effects will allow clinicians and women of childbearing age to make more informed decisions regarding the use of medications during pregnancy.

833. Abstract withdrawn by author.

834. Predicting Enrollment and Study Duration in Pregnancy Exposure Registries

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Background: Pregnancy registries are important tools to examine drug safety in pregnancy. Because pregnancy registries are unique, they present challenges in estimating critical factors impacting enrollment and study duration, including accrual, retention, and live birth (LB) rates.

Objectives: To examine: (1) critical factors in ongoing pregnancy registries and estimate impact on sample size and enrollment duration; and (2) drug prescribing patterns in pregnancy in the National Ambulatory Medical Care Survey (NAMCS) and correlate with pregnancy registry enrollment.

Methods: We examined published data from pregnancy registries identified through internet and literature searches. Of the 58 pregnancy registries identified, only 18 published sufficient detail to allow calculation of LB, retention, and accrual rates. We also examined data from NAMCS, a representative sample of US ambulatory visits capturing medications prescribed in 2.5 million pregnancies.

Results: The median LB rate for ongoing pregnancy registries was 88% (range: 62–95%). Median retention was 73% (range: 37–99%), and median annual accrual was 81.9 (range: 5.3–296). Using median rates, 422 pregnancies enrolled over 5 years would yield sufficient power to rule out a doubling in risk of birth defects. Rates varied from a low of 320 pregnancies enrolled over 1.1 years to a high of 570 enrolled over 50+ years. In NAMCS, frequently prescribed drugs included prenatal vitamins and drugs indicated in pregnancy as well as antimicrobials, antidepressants, and drugs to treat diabetes, asthma, allergy, epilepsy, and herpes. Correspondingly, the highest enrolling pregnancy registries were for drugs to treat depression, epilepsy, and herpes. Other factors impacting enrollment were population, design, and recruitment-retention activities.

Conclusions: LB rate was the least volatile factor examined and accrual was the most volatile. Using observed rates in pregnancy registries may aid in determining enrollment and duration, but these rates are highly variable. Examining prescribing patterns in pregnancy from national data sources can also aid in predicting enrollment. Careful consideration should be given to other factors that could impact enrollment.

835. Trends in Medication Use in Pregnancy over a 1 Years Period

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Background: In recent years more attention has been paid to improving access to data on the safety of medication use in pregnancy. It is not known if this increased attention has led to changes in prescribing habits of medications in pregnancy.

Objectives: To examine trends over a 10 years period in prescribing patterns of medications in pregnancy in a nationally representative sample of ambulatory care visits in the US.

Methods: We examined data from the National Ambulatory Medical Care Survey (NAMCS) from 1998 to 2008. The dataset captures medications prescribed or supplied at each visit. National estimates are based on visit weights provided by the National Center for Health Statistics.

Results: In 1998, women of child-bearing potential (WCBP) made approximately 193 million office visits, and 18% of visits were made by pregnant women. In 2008, the number of visits by WCBP increased slightly to 194 million, but the percentage of visits made by pregnant women decreased to 13%. In 1998 at least one medication was prescribed on 41% of visits made by pregnant women. This increased to 60% in 2008. The most common classes of drugs prescribed in 1998 were prenatal vitamins or supplements, hematologic agents, and antimicrobials. Drugs contraindicated in pregnancy (Category X) were prescribed in 1% of visits. As expected, prenatal vitamins were still the most commonly prescribed medications in 2008. The next most commonly prescribed were antimicrobials, heartburn medications, and antidepressants. Hematologic agents were rarely prescribed. Within each class, drugs with little or no known risk (Category B or C) were preferentially prescribed over drugs with known human risk (Category D or X). In a few instances Category D drugs were prescribed rather than a Category B or C. Rarely was a Category X drug prescribed in 2008.

Conclusions: The percentage of visits in which at least one medication was prescribed or supplied to pregnant women increased substantially between 1998 and 2008. There was a decreasing trend over the study period in the percentage of Category X drugs prescribed. However the percentage of antidepressants increased despite widespread concerns about the safety of these drugs in pregnancy.

836. Pregnancy Prevention Programs (PPPs) in the EU

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Background: A PPP is implemented to eliminate the risk of on birth defects due to intra-uterine drug exposure by preventing pregnancies. In the EU, seven drugs have a PPP: thalidomide and lenalidomide, retinoids: acitretin, isotretinoin, and alitretinoin, and endothelin receptor antagonists (ERAs) bosentan and ambrisentan.

Objectives: To identify the background of the PPPs, to compare the PPPs, and to identify possibilities for harmonisation.

Methods: For each drug the active substance, indication, authorisation date, authorised age and gender of the users, duration of use and drug half life were identified from the Product Information (PI). Literature was used to describe the actual population of use (including gender and age distribution). Patient exposure in the Netherlands was estimated using two databases, the information system of the Health Care Insurance Board (2006–2010) and the IADB.nl (1999–2009). The elements of the PPPs were identified from the PI.

Results: Thalidomide/lenalidomide (indicated for multiple myeloma; median age 71 years) and the retinoids (indicated for severe acne, psoriasis or hand eczema occurring at 15–30 years) have a high teratogenic risk in humans. The ERAs (indicated for pulmonary arterial hypertension (PAH); mean age 52 years) were teratogenic in rats; relevance to humans is unknown, but PAH is associated with high mortality in mothers during and shortly after pregnancy. Total patient exposure in the Netherlands for thalidomide, lenalidomide, bosentan or ambrisentan is ≤1,000 patients per year, orphan indications. Five thousand patients per year were exposed to acitretin and 20,000 per year to isotretinoin of which approximately 30% women of childbearing potential. Similarities in the PPPs were: pregnancy tests before, during and after drug use; minimal one effective contraceptive. Differences were seen with educational materials for physicians, pharmacists or patients, restricted drug supply, patient card, and patient registry.

Conclusions: PPPs should be implemented for drugs with a high human teratogenic risk, although exposure in women of childbearing potential is low. Elements of PPPs should be harmonised and differences limited.

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837. Prescription Drug Use among Pregnant Women in Opioid Maintenance Treatment

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Background: Pregnant women in Opioid Maintenance Treatment (OMT) experience increased risk of adverse pregnancy outcomes. Additional use of other prescription drugs may further increase this risk. Knowledge about prescription drug use in this vulnerable patient group is very limited.

Objectives: Describe prescription drug use among women in OMT prior to and during pregnancy. Describe neonatal outcomes following OMT during pregnancy compared to other neonates.

Methods: Cohort study based on linkage of two nationwide databases: the Medical Birth Registry of Norway and the Norwegian Prescription Database.

Setting: The first singleton pregnancy of all Norwegian women who lived in Norway at the time of birth (2004–2008) were included (N = 194,935). Women that were dispensed methadone mixture, buprenorphine or buprenorphine-naloxone combined sublingual tablets from pharmacies during pregnancy (n = 95) were identified as OMT women.

Main Outcome measures: Prevalence of prescription drugs dispensed 3 months prior to and during pregnancy. Dispensed amounts of benzodiazepines, z-hypnotics and opioid analgesics were studied in detail. Neonatal outcomes in OMT women and all other pregnancies were identified.

Statistical analysis: Descriptive statistics. Fischer exact test were used to compare proportions of neonatal outcomes.

Results: Eighty-eight percent of the pregnant women were dispensed other prescription drugs than OMT. The proportion of women who were dispensed drugs acting on the nervous system (43%, 95% CI 33–53) and/or antiinfectives (52%, 95% CI 41–63) during pregnancy was especially high. Use of prescription drugs with abuse potential was reduced from prior to pregnancy and throughout pregnancy. Only 3% of the OMT women were dispensed antidepressants. The neonates born of OMT women had lower gestational age, birth weight and length and head circumference than other neonates.

Conclusions: Pregnant women in OMT in Norway used high amounts of prescription drugs, but reduced their use of drugs with abuse potential as pregnancy proceeded. Low use of antidepressants indicated that women in OMT in Norway may be undertreated for depression.

838. Major Malformations in Babies Whose Mothers Had Pre-Existing Diabetes during Pregnancy

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Background: Pregnancy outcomes in women with pre-existing diabetes are known to be worse than in the healthy population: rates of congenital malformations have been reported to be 2 to 10-fold higher. This is due to poor glycaemic control.

Objectives: To determine rates of congenital malformations in babies of mothers with type1 (DM1) and type2 (DM2) diabetes and compare with the healthy population.

Methods: Patients with pre-existing DM1 or DM2 during pregnancy were identified on the General Practice Research Database using diagnoses, prescribing, use of testing equipment and referral records. Mothers were matched to babies using registration records with the same family number, within 2 months of delivery date. Major congenital malformations were identified in the baby's record and malformations verified with at least two related medical records; free text entries were checked.

Results: Between January 1992 and March 2007 1,057 DM1 patients had 1,329 pregnancies and 365 DM2 patients had 441 pregnancies that resulted in a live birth. Eighty-four major malformations were found in 78 babies of DM1 mothers: 41 were cardiac, 11 were urogenital and eight were limb defects. Twenty-six major malformations were identified in 22 babies of DM2 mothers (seven cardiac defects). Overall, 5.9% of babies of DM1 mothers and 5.0% of babies of DM2 mothers had a malformation compared to 2–3% in the healthy population. The malformation rate for babies of DM2 mothers was comparable with another study (5.8%) but was lower for DM1 (8.2%). The proportion of cardiac malformations in babies of DM1 mothers was three times higher than in the healthy population.

Conclusions: Babies whose mothers had DM1 or DM2 during pregnancy had double the rate of malformations. Pregnancy loss due to malformation has not been included but previous work found a greater proportion of terminations for medical reasons (1% in DM1, 1.8% in DM2) compared to healthy pregnancies (0.8%). Limitations include potentially differential recording of malformations between babies of mothers with DM1 and DM2 and the lack of records of glycaemic control. Differences in rates of malformations between treatments including analogue and human insulin will be evaluated next.

839. Methodology on Study Using Administrative Data of Selective Serotonin Reuptake Inhibitors during Pregnancy and the Risk of Infants

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Background: There is ongoing debate about the safe use of selective serotonin reuptake inhibitors (SSRIs), widely prescribed for management of depression during pregnancy. Incidence of antenatal depression was estimated to be 6% in Japan, and research using a large administrative data is needed for drug safety utilization.

Objectives: To summarize methodologies for evaluating pregnancy outcomes associated with SSRIs from existing pharmacoepidemiology studies for developing a study using a Japanese insurance claims database.

Methods: Medical literature review was conducted using PubMed to identify all articles using administrative data and assessing the risk of congenital malformations in infants whose mother was taking SSRIs during pregnancy. Information on study designs, definitions of drug exposure and outcome, and limitations was summarized.

Results: Four studies were selected for the analysis: three retrospective cohort studies and one nested case–control study. To define timing of drug exposure, some studies estimated a gestational age from last menstrual period (LMP) and others evaluated it with the assumption of a gestational age of 270 days, with three 90-day trimesters of pregnancy. Sometimes dosages of drug exposure were incompletely evaluated. To define outcomes, some studies targeted one certain malformation and others targeted all malformations identified by diagnosis and/or procedure codes. Information of individual characteristics including race, smoke, alcohol, and body mass index was usually not included in the administrative database and must be linked with other data for adjusting the potential confounding factors.

Conclusions: To compare with existing studies, advantages of using the Japanese administrative database including information on gestational age, dosage of medicine and outcomes coded by diagnosis and procedure codes were identified. However, a fundamental limitation of lacking information on potential confounders was still remained. Hence a well-designed research is needed to minimize potential biases using the Japanese administrative data.

840. Drugs Associated with Teratogenic Mechanisms: Prescription Rates among Pregnant Women and a Systematic Review of Effects

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Background: Previously, the main teratogenic mechanisms of medical drugs were described, but insight in the use of prescription medication associated with these mechanisms and knowledge on the human teratogenic effects of these drugs are lacking.

Objectives: To determine prescription rates of drugs associated with the teratogenic mechanisms described previously among pregnant Dutch women and to evaluate the current knowledge on the human teratogenic risks of these drugs.

Methods: We estimated prescription rates of the medical drugs involved among pregnant women living in the Netherlands using data from the IADB.nl database. In addition, time trends in prescription rates were evaluated. Furthermore, we conducted a systematic review of the literature to study the human teratogenic effects of these medical drugs. Of 13,771 potential articles, 247 were included in the systematic review.

Results: In 177 per 1,000 pregnancies in our study population at least one drug associated with a teratogenic mechanism was dispensed in the first trimester. The prescription rates increased over time for vasoactive drugs, selective serotonin-reuptake inhibitors (SSRIs), and serotonin receptor agonists/antagonists. Epidemiologic studies that assessed the teratogenic risks were identified for less than half of the drugs included in the study. For a number of drugs, including acetaminophen, aspirin, antihypertensive medication, the antiepileptic drugs carbamazepine, phenobarbital, and valproic acid, clomiphene, and some SSRIs, in particular fluoxetine and paroxetine, associations between exposure in early pregnancy and specific birth defects were observed in both cohort and case–control studies. However, for most drugs and drug groups, the numbers of exposed infants were too small to draw any conclusions regarding their human teratogenic risks.

Conclusions: Although prescription medication is frequently used in the first trimester of pregnancy, evidence for the presence or absence of human risks of birth defects is scarce or non-existent for the majority of medical drugs associated with teratogenic mechanisms.

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841. Prenatal Use of Medicines and Substances: Prevalence and Assessment of Mothers' Safety Knowledge

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Background: Pregnancy is a time of vulnerability and as such the use of medicines and substances during this period presents a special concern due to the potential for adverse effects in the unborn child. Therefore an approach which expands existing research is critical to estimate the prevalence of medicine and substance use; evaluate the mothers' safety knowledge and to make the resulting information available to stakeholders so that it contributes to safe and effective healthcare.

Objectives: To estimate the prevalence of prenatal medicine and substance use and assess mothers' safety knowledge.

Methods: This longitudinal study is being carried out in two London teaching hospitals. Pregnant women on appointment for their first trimester scan were consecutively recruited and interviewed with a structured questionnaire about their medicine and substance use (licit illicit) and their safety knowledge. The inclusion criteria were women over 16 years who could communicate in English. This study was approved by the ethics committee and follow-up of the women is on-going.

Results: Of the 436 women that were approached, 400 participated and their age was 31.8 ± 5.2. Ninety-nine percent of them had used at least one medicine or substance in the first trimester; 40.5% used prescription medicines, 83.8% used over-the-counter medicines, 36% used complementary alternative medicines, 12% took alcohol, 0.5% used cannabis and 3% smoked cigarettes. In terms of information on the safety of medicines and substances in pregnancy, 36.2% reported having insufficient information about prescription medicines, 36.7% felt they had insufficient information about over-the-counter medications and 55.2% thought they had insufficient information about complementary alternative medicines. Finally 95.3% reported having enough information about licit drugs and 78% felt they had enough information about illicit drugs.

Conclusions: The results indicate that medicine use in pregnancy is common but a considerable number of women felt they have insufficient information about safety of medicines. Healthcare providers should make efforts to protect women and unborn babies by providing evidence-based counselling.

842. Patterns of Medication Use during Pregnancy and Prevalence of Birth Defects in a Large Administrative Claims Database

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Background: Administrative claims databases may serve as pharmacovigilance tools for exposures during pregnancy given the capture of medication dispensings as well as maternal and neonatal outcomes in large populations.

Objectives: The aim of this analysis was to describe mother-infant pairs in a large insurance claims database with respect to maternal characteristics, medication use during pregnancy and frequency of birth defects.

Methods: This was a descriptive study of mother-infant pairs identified from 2001 to 2011 in the HealthCore Integrated Research Database (HIRD^{SM}), a US commercial insurance claims database. We characterized pairs with respect to maternal factors and patterns of medication use during pregnancy by trimester. We also compared the computed prevalence of selected birth defects in the HIRD to published national estimates.

Results: We identified 696,201 infants born to 600,275 mothers (15.1% of mothers delivered >1 infant). Mothers had a mean age of 30.8 ± 5.1 years, and 61.3% were enrolled in the health plan for ≥12 months prior to delivery. Prior to pregnancy, 2.2% of mothers were diabetic and 1.5% had hypertension. Of the infants, 7.5% were premature and 7.1% were twins or other multiples. The most common classes of medications dispensed during pregnancy were analgesics, antiasthmatics and antidepressants. There was a strong increasing trend in first trimester use of anticonvulsants, vaccines and antihypertensives over time. The estimated prevalence of birth defects over the study period was much higher than published estimates at 580 per 10,000 live births. An increasing temporal trend was observed for certain cardiovascular and genitourinary anomalies. When compared to national estimates, the largest differences were observed for cardiovascular anomalies, with higher prevalence observed in the HIRD.

Conclusions: Large insurance claims databases can be useful for monitoring birth defects and medication usage during pregnancy. However, additional research is required to understand observed differences in the frequency of certain types of defects when compared to national estimates.

843. Drug Use and Spontaneous Abortion: A Case/Control Study

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Background: Few studies have been conducted to investigate drug effects on miscarriage risk.

Objectives: The objective of the present study was to evaluate the association between first trimester drug exposure and miscarriage occurrence.

Methods: We performed a nested case–control study using data from Terappel, a French database which records since 1984 requests from health professionals to Regional Centers of Pharmacovigilance about women exposed to drugs during pregnancy and which registers corresponding pregnancy outcomes. Cases were women who had a clinically detected miscarriage (before the 22th week of amenorrhea) and controls were women who gave birth to a child. Drug uses since the beginning of pregnancy were compared between cases and controls during the same period of pregnancy. Odds ratios were calculated by means of a multivariate logistic regression analysis adjusted for age.

Results: Of 838 cases and 4,508 controls were identified in the database. Miscarriage was reported on average at 9.4 (±3.0) weeks of amenorrhea. In controls, the length of gestation was 38.9 (±2.0) weeks of amenorrhea. Cases were older than controls (32.4 [±6.1] vs. 30.6 [±5.4] years; $p < 0.0001$). Cases were more exposed than controls to "Tricyclic antidepressants" (ATC code: N06AA) (4.7% vs. 2.0%; OR = 2.2 [CI95% 1.5–3.3]), "Anti-protozoals" (ATC code: P01) (3.8% vs. 2.4%; OR = 1.6 [CI95% 1.02–2.4]) and "Centrally acting anti-obesity products" (2.5% vs. 0.6%; OR = 3.4 [CI95% 1.9–6.2]). Inversely, controls were more exposed than cases to H1 antihistamines (4.5% vs. 2.9%; OR = 0.6 [CI95% 0.4–0.9]).

Conclusions: The few literature data do not suggest a positive link between miscarriage risk and "Tricyclic antidepressants", "Anti-protozoals" and "Centrally acting anti-obesity products" exposure but protopathic bias is possible. About the potential protective effect of H1 antihistamines on miscarriage risk, we have been unable to locate pharmacoepidemiological studies reporting such a result. However, this result could be explained by a physio-pathological mechanism since animal and clinical experimental studies have suggested links between hyperhistaminemia and gestational complications such as miscarriage.

844. National Birth Defects Prevention Study – Medication Results Published in 2004–2011

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Background: The National Birth Defects Prevention Study (NBDPS) is a population-based, case–control study of major birth defects in the United States. This ongoing study began in 1997 and, to date, 125 papers have been published. The current review examines NBDPS results pertaining to medication use in pregnancy.

Objectives: (1) graphically summarize all published NBDPS results; (2) identify exposure-birth defect combinations that have not been assessed yet; and (3) guide the direction of future birth defects research.

Methods: Adjusted odds ratios and corresponding 95% confidence intervals were abstracted from published papers that used data pooled from all study centers. Birth defect groups included infants with both isolated and multiple defects. Papers limited to non-birth defect outcomes and NBDPS methods were excluded from this review. Also excluded were results not pertaining to each paper's main exposure(s) of interest. The birth defects-exposure matrix is a graphical summary of these results. Cells on the matrix are color-coded based on all published NBDPS results for each association taking into account the results' consistency, direction, and statistical significance.

Results: To date, 25 papers have been published by the NBDPS examining the association between maternal medication use and risk for birth defects. Data from the NBDPS have confirmed previous findings (e.g., trimethoprim and birth defects); have identified associations not reported before (e.g., nitrofurantoins and anopthalmia/micropthalmia); and have shown specific medications to not be associated with the studied birth defects (e.g., fexofenadine).

Conclusions: Although some medications were found to be associated with birth defects, results from the NBDPS indicate that medications most commonly taken during pregnancy are generally not associated with birth defects. Future research should focus on exposures that have not been extensively studied such as corticosteroids, diuretics, and decongestants, as well as confirm some of the new findings identified in the NBDPS. This review also stressed the importance of assessing individual birth defects instead of all birth defects combined.

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845. Prescription Drugs in Pregnancy: A UK Primary Care Study

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Background: Prescription drugs are commonly used during pregnancy. However, the use of specific medications changes across populations and over time.

Objectives: To provide information on the prevalence of use of prescription drugs during the first trimester of pregnancy as well as to study temporal trends during the last decade in the UK.

Methods: We used electronic medical records from The Health Improvement Network (THIN) from 1996 to 2010 to identify completed pregnancies. The study cohort included the first pregnancy identified during the study period in women 13–49 years old who were enrolled with their primary care physician for at least 1 year before the last menstrual period (LMP) to delivery. Gestational timing was based on LMP date and, when LMP was missing (41.4% of pregnancies) we used a computerized algorithm with a hierarchical sequence to estimate gestational timing. We linked mother and baby records by means of the family identification number. Prescription of specific drugs during the first trimester and time trends during the last decade were evaluated.

Results: Among 148,544 completed pregnancies identified (89% linked with offspring), the most commonly prescribed drugs during the first trimester were antibiotics (amoxicillin prescribed to 5.2%), asthma/allergy medications (salbutamol to 3%), analgesics (acetaminophen to 3.7%) and antidepressants (fluoxetine to 1.0%). From 1996 to 2010, the proportion of women with at least one prescription during the first trimester increased for most drug classes, markedly for antidepressants (1.8–4.2%) hypoglycemic agents (0.3–1.0 %), DMARDs (0.04–0.18%), opioids (1.5–2.6%) and thyroid hormones (0.7–1.6%); while antibiotics and analgesics remained stable. Overall, the prevalence of prescriptions for contraindicated drugs during pregnancy was below 4 per 1,000 pregnant women.

Conclusions: Given the widespread use of prescription medications during the first trimester of pregnancy, and its raise during the last decade, further studies are needed to understand the safety of these medications for the mother and the developing fetus.

846. Fetal Safety of an Adjuvanted Influenza A(H1N1)pdm09 Vaccine

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Background: Assessment of the fetal safety of vaccination against influenza A(H1N1)pdm09 in pregnancy has been limited to pharmacovigilance reports and descriptive studies.

Objectives: To investigate whether exposure to an adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy was associated with increased risk of adverse fetal outcomes.

Methods: Registry-based cohort study based on all live-born singleton infants in Denmark, delivered between November 2009 and September 2010. In propensity score-matched analyses, we estimated prevalence odds ratios (PORs) of adverse fetal outcomes, comparing infants exposed and unexposed to an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy.

Results: From a cohort of 53,432 infants (6989 [13.1%] exposed to the influenza A(H1N1)pdm09 vaccine during pregnancy), 660 (330 exposed) were included in propensity score-matched analyses of adverse fetal outcomes associated with first trimester exposure and 13,284 (6,642 exposed) in analyses of second or third trimester exposure. A major birth defect was diagnosed in 18 (5.5%) of 330 infants exposed to the vaccine in the first trimester, compared with 15 (4.5%) of 330 unexposed (POR 1.21, 95% confidence interval [CI] 0.60–2.45). Preterm birth occurred in 31 (9.4%) of 330 infants exposed in the first trimester, compared with 24 (7.3%) of 330 unexposed (POR 1.32, 95% CI 0.76–2.31), and in 302 (4.6%) of 6,543 with second or third trimester exposure compared with 295 (4.6%) of 6,366 unexposed (POR 1.00, 95% CI 0.84–1.17). Small for gestational age was observed in 25 (7.6%) of 330 infants with first trimester exposure, compared with 31 (9.4%) of 330 unexposed (POR 0.79, 95% CI 0.46–1.37), and in 641 (9.7%) of 6,642 with second or third trimester exposure compared with 657 (9.9%) of 6,642 unexposed (POR 0.97, 95% CI 0.87–1.09).

Conclusions: In this Danish cohort, exposure to an adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy was not associated with a significantly increased risk of major birth defects, preterm birth, or fetal growth restriction.

847. Validation of an Algorithm Ascertaining Cases of Osteonecrosis of the Jaw in the Swedish National Patient Register

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Background: Osteonecrosis of the jaw (ONJ) is a medical condition associated with antiresorptive drugs, among others used to treat osteoporosis. Currently, there is no consensus regarding the definition of ONJ, and no ONJ-specific ICD code exists. Therefore, register-based studies of this condition may be troublesome.

Objectives: To validate an algorithm ascertaining ONJ cases, in an attempt to facilitate future epidemiological assessments of ONJ.

Methods: By means of the Patient Register and the Prescribed Drug Register we identified women 55 years or older with osteoporosis, an osteoporotic fracture or osteoporotic medication, 2005–2010. To find potential cases of ONJ, we employed an algorithm including the following diagnoses: periapical abscess with sinus, inflammatory conditions of jaws, alveolitis of jaws, idiopathic aseptic necrosis of bone, osteonecrosis due to drugs, osteonecrosis due to previous trauma, other secondary osteonecrosis, other osteonecrosis, and unspecified osteonecrosis. Women seen at oral and maxillofacial surgery departments, with at least one of the diagnoses, were classified as potential cases of ONJ. Validation was done through medical record review. Case confirmation was based on the ONJ definition by the American Association of Oral and Maxillofacial Surgeons. The algorithm was evaluated by positive predictive values (PPVs) stratified by diagnosis.

Results: For 87 potential cases identified nationally through our algorithm, medical records were obtained for 83. The overall PPV was 18% (95% confidence interval [CI] 10–28%). The highest PPV was observed in osteonecrosis due to drugs (83%, 95% CI 36–100). Several diagnoses had a PPV of 0 or were not used at all (periapical abscess with sinus, alveolitis of jaws, idiopathic aseptic necrosis of bone, osteonecrosis due to previous trauma, other secondary osteonecrosis, other osteonecrosis and unspecified osteonecrosis).

Conclusions: It is possible to ascertain cases of ONJ from the Swedish registers using this algorithm, however, the PPV is low. Thus, further refinements of the algorithm are necessary.

848. Positive Predictive Value for Upper Gastrointestinal Bleeding in Four Health Care Databases Using Different Coding Systems in the EU-ADR Project

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Background: For active product surveillance with automated safety signal detection it is necessary to assess the accuracy of diagnosis codes of upper gastrointestinal bleeding (UGIB) in health care databases (DBs).

Objectives: We evaluated the accuracy of codes and free text search for identification of patients with UGIB.

Methods: Four DBs were used: (1) IPCI (Netherlands); (2) HSD (Italy); (3) Tuscany Regional DB (Italy); and (4) Danish National Registry of Patients (Denmark). The first two were medical record databases from primary care (PC), the latter ones were administrative DBs. Three diagnosis coding systems were used: (1) International Classification of Diseases (ICD-) 9th revision (HSD + Tuscany); (2) ICD-10th revision (Denmark); and (3) International Classification of PC (ICPC) (IPCI). Additionally, free text search was conducted in IPCI and HSD. We identified patients using UGIB-specific codes (ICD-10: K25-29, K92.0, K92.1, K92.2; ICD-9: 531–535,578; ICPC: D14, D15, D85, D86) or key words as identified by UMLS mapping. From all identified UGIB cases 200 were randomly selected from each DB and reviewed manually by medically trained assessors. The UGIB cases were classified as definite, non-assessable, or non-case. For each database positive predictive values (PPV%) were calculated.

Results: For IPCI, 70% of patients were identified via searches of diagnoses words in narratives. Upon review of the medical charts, 37 patients were classified as confirmed UGIB case, resulting in a PPV of 18.6 (CI: 13.2–24). PPV was 18.8 (CI 12.3–25.4) and 16.7 (CI 7.2–26.1) for free text and codes respectively. For HSD, 70% of patients were identified via codes. The overall PPV was 80.7 (CI: 74.7–86.8); the PPV increased to 89.1 (CI: 83.5–94.7) for codes and decreased to 57.1 (CI: 42.2–72.1) for text only. The overall PPV for Tuscany was 76.8 (70.7–82.8). For Denmark, a PPV of 72.9 (CI 65.9–79.9) was estimated.

Conclusions: The accuracy of automated case identification of UGIB patients varies across databases depending on DB-specific coding system, use of free text and severity of the event being captured (hospitalized vs. non-hospitalized).

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849. Validation of Cataract Diagnosis in the UK General Practice Research Database

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Background: The General Practice Research Database (GPRD) is widely used for pharmacoepidemiologic research. The validity of several GPRD Read code definitions have been demonstrated, however, to our knowledge, Cataract diagnoses recorded in GPRD has not been validated to date.

Objectives: To determine (1) the positive predictive value (PPV) of multiple Read codes identifying incident cataract cases in General Practice Research Database (GPRD); (2) the ability to capture the correct timing of the clinical event; (3) the sources of data that GPs rely on to validate the diagnosis.

Methods: Patients in GPRD with read codes suggesting a diagnosis of cataract, between 1 January 1990 and 31 December 2010, were identified as potential cases. Among these cases, a total of 1,000 records were randomly selected for validation. Questionnaires were sent to the general practitioners (GP) to verify the diagnosis, the timing of the diagnosis, and to collect other supporting information.

Results: To date, a total of 514 questionnaires have been received back from GPs. Of 57.8% (297/514) of returned questionnaires provided supporting documents that had been used to verify the diagnosis by the GP. The PPV of the cataract read codes was 91.8% (472/514), of which 294 cases were diagnosed by an ophthalmologist. Among confirmed cases, 98 (20.7%) had a different diagnosis date than the one recorded in the electronic medical records (EMR). The median difference in timing was 140 days; 35 (35.7%) of the dates had >1 year difference. The sources of data that GPs rely on to validate the diagnosis included paper medical charts (7%), hospital/surgical records (16.3%), consultation and/or outpatient letters (62.3%), and GP's clinical notes (43.6%).

Conclusions: High PPV suggests that GPRD Read codes are sufficient to identify cataract cases, however, the accuracy of the diagnosis timing is difficult to determine. Therefore, studies investigating the association between drug exposure and cataract in GPRD should consider methods such as lagged exposure time for the main or sensitivity analysis.

850. Validation of Glaucoma Diagnosis in the UK General Practice Research Database

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Background: The General Practice Research Database (GPRD) is widely used for pharmacoepidemiologic research. The validity of several GPRD Read code definitions have been demonstrated, however, to our knowledge, glaucoma diagnoses recorded in GPRD has not been validated to date.

Objectives: To determine (1) the positive predictive value (PPV) of multiple Read codes identifying incident glaucoma cases in General Practice Research Database (GPRD); (2) the ability to capture the correct timing of the clinical event; and (3) the sources of data that GPs rely on to validate the diagnosis.

Methods: Patients in GPRD with read codes suggesting a diagnosis of glaucoma, between 1 January 1990 and 31 December 2010, were identified as potential cases. Among these cases, a total of 1,000 records were randomly selected for validation. Questionnaires were sent to the general practitioners (GP) to verify the diagnosis, the timing of the diagnosis, and to collect other supporting information.

Results: To date, a total of 751 questionnaires have been received back from GPs. Of 63% (473/751) of returned questionnaires provided supporting documents that had been used to verify the diagnosis by the GP. The PPV of the glaucoma read codes was 83% (623/751), of which 556 cases were diagnosed by an ophthalmologist. Among confirmed cases, 215 (34.5%) had a different diagnosis date than the one recorded in the electronic medical records (EMR). The median difference in timing was 325 days; 102 (16%) of the dates had >1 year difference. The sources of data that GPs rely on to validate the diagnosis included paper medical charts (8.8%), hospital/surgical records (17.8%), consultation and/or outpatient letters (72.9%), and GP's clinical notes (40.6%).

Conclusions: High PPV suggests that GPRD Read codes are sufficient to identify glaucoma cases, however, the accuracy of the diagnosis timing is difficult to determine. Therefore, studies investigating the association between drug exposure and glaucoma in GPRD should consider methods such as lagged exposure time for the main or sensitivity analysis.

851. Abstract withdrawn by author.

852. Safety Montiroing – Linking Databases Creating Metrics

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Background: Never in the history of Life Sciences industry was need of fundamentally relooking at the strategy of Safety Management as it is now. The reasons vary from significant increase in AERS reported to FDA, increase of SAE in spite of risk management programs, more people reporting AE, MA etc. This has direct impact on how Life Sciences companies define, understand, evaluate and control their Safety departments. Historical view of looking at operational aspects is no longer seen as a competitive advantage or element of improvement. At the same time standards of evaluating strategic elements are still evolving and maturity is quite varied across the industry.

Objectives: In new paradigm, goals objectives of pharmacovigilance system would be twofolds.

1. Quality compliance
2. Add value to the core business of pharma

Methods: A new system method is proposed to link different ystems on CAPA, Adverse Event Reporting Systems, Regulatory Submission, Clinical Safety, PK-PD, Pre-clinical ADME to measure report metrics. A well defined and quality metric is of useful when it is applied business logic to generate a KPI that is able to a "value" anywhere from an operational excellence to a strategic one. The value drivers can be categorized in the one of the following: Regulatory strategy/policy definitions, Product commercialization, Compliance, Quality and Training/Learning.

Results: Safety KPI Metrics are graphical representation (through bar graphs pie charts) of key data points based on safety data. This is definition is theoretical, however, what is more important is to have a practical approach of "how" the metrics will be captured, what are the "types" of metrics, how can we ensure the "quality" of metrics is worthy and map metrics with "stakeholders" of Safety organization. Out of the many approaches researched, we believe that the best way to define Safety Metrics is to use proven concepts from Metrics Champion Consortium.

Conclusions: Once the business case for Safety Metrics is in place, it will be important for a Safety Organization to define an IT enabled solution (data processing layer as well as aggregation layer for decision support), with a well understood roadmap to adopt the solution.

853. Accuracy of Coding-Based Algorithms in Identification of Acute Myocardial Infarction from Multi-Country Electronic Healthcare Records (EHR) Databases

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Background: Accuracy of outcome ascertainment is crucial to ensure validity when mining multiple electronic healthcare records (EHR) databases for drug safety signal detection.

Objectives: To evaluate the accuracy of various coding algorithms used to identify cases of acute myocardial infarction (AMI) from three European EHR databases

Methods: We conducted a validation study in three databases of the EU-ADR network: (1) IPCI (GP database, NL); (2) HSD (GP database, Italy); and (3) Aarhus (claims, Denmark). We identified cases of AMI from GP medical records, primary hospital discharge diagnoses, and death registries using coding algorithms that employed three different disease terminology schemes: (1) ICPC); (2) ICD9-CM; and (3) ICD-10. We also used free text using key words consistent with AMI. A random sample of 200 cases per database was obtained from all potential cases identified. Additional 200 cases identified by free text search were obtained. Review of medical records and hospitalization charts was performed using standardized questionnaire implemented as computerized data entry using custom-built software Chameleon© locally installed in each database. Positive predictive values (PPV) were calculated overall and for each code and free text query.

Results: The study population comprised EHR data from 4,034,232 individuals with 22,428,883 person-years of follow-up in the period 1995–2011. Within this population, a total of 42,774 potential cases of AMI were identified. From the random sample of 800 potential cases of AMI selected for validation, 748 records were retrieved (93.5%) and reviewed. All ICD-10 codes used had 100% PPV. Overall the ICD9-CM codes had very good PPV, with the most frequently occurring code having PPV of 96.5% (95% CI 93.5–100.4). ICPC code-based algorithm had PPV of 75% (67.4–82.6). Use of free text had lower PPV: 60% (17.1–102.9) in HSD and 19.7% (12.9–26.5) in IPCI.

Conclusions: The results obtained in this study are consistent with PPV estimates for ICD9-CM and ICD-10 cited

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in the literature. Strategies are necessary to further optimize the value of free text search in the identification of AMI in EHR databases.

854. Using an Automated Computer-Based Algorithm To Increase the Efficiency of Selecting the Best Match from National Death Index Linkage Results

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Background: Researchers often use the National Death Index (NDI) for death tracing of study subjects. NDI can return multiple potential matches for an individual, which may require manual review to determine the most likely match. This ongoing drug safety study uses claims data maintained in a distributed common data model by 12 large health insurers/data partners (DP), with central programming provided to the DPs for analyses. DPs submit a large number of study subjects to NDI and may receive a very large number of potential matching deaths overall. Central programming of a common automated algorithm (AA) designed to select the most likely true match for each patient provides an opportunity to make the review of NDI results transparent, consistent, and efficient.

Objectives: To describe the AA used, evaluate the efficiency of this approach, and contrast this approach with NDI's standard approach to selecting the most likely true match.

Methods: DPs will submit identifiers from study subjects to NDI for death tracing. DPs will apply a centrally developed AA to assess the large number of overall possible matches identified by NDI to select the most likely true match for each patient. The AA is based on an algorithm used widely by US cancer registries.

Results: We will describe the number of patients submitted by type (vital status known vs. unknown); the average number of potential matches NDI returned per patient; the total number of true matches by type of user record using the AA vs. NDI matching methodology; the proportion of AA-defined matches for which cause of death was provided (NDI assigned the match a high enough probabilistic score to be considered a "true match; assumed dead"). We will also discuss logistic challenges and whether the AA eliminates the need for manual review.

Conclusions: The application of a standard AA to assess many potential NDI matches represents a promising approach for increasing the efficiency, reducing the research burden, and standardizing the evaluation of NDI results in the context of large, multisite, complex research collaborations.

855. Identification of Patients with Diabetes Mellitus Type 2 in insurance Claims Data – Are Problems Caused by Ambiguous ICD-10 Codes?

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Background: Claims databases reflect routine medical care in broad populations and provide a valuable basis for studying the effects of antidiabetic treatments in patients with diabetes mellitus (DM). However, a reliable strategy is needed to discriminate between patients with type-2 and type-1 DM in these databases.

Objectives: To assess the coding quality of diabetes diagnoses and the prescription patterns of antidiabetic treatment to identify patients with DM2 in insurance claims data.

Methods: Data from three German statutory health insurances were used to identify patients with diabetes diagnoses or prescriptions of antidiabetics. The coding quality was evaluated regarding diabetes type and consistency over time. We used a DM2 specific treatment pattern consisting of treatment with oral antidiabetics (OAD) followed by insulin initiation to detect insulin-naive DM2 patients by prescriptions. The antidiabetic treatment pattern was assessed in this population.

Results: Among 7.43 million insurants, 579,953 (7.8%) had a diabetes diagnosis and 259,488 (3.5%) were treated with antidiabetics. The majority of diagnoses (56.5%) was related to DM2 followed by unspecific codes (30.9%). We observed major coding inconsistencies including different diabetes types in the same patient (45.6% of patients) and 4,964 patients with malnutrition-related DM. In contrast, the prescription pattern of antidiabetic treatment in insulin-naive patients was in line with national guidelines for treatment of DM2.

Conclusions: Considering the specific treatment pattern for DM2, the identification of DM2 patients in claims data is more reliable based on prescriptions than on diagnosis codes. The poor coding quality may result from the ambiguous labelling of ICD-10 codes for diabetes.

856. Deterministic Linkage between Cystic Fibrosis Patient Registry Data to Medicaid Analytical Extract Data

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Background: Medicaid (MAX) data contain comprehensive reimbursed health services claims but lack clinical parameters. The National Cystic Fibrosis (CF) Registry (NCFR) collects clinical information but provides quarterly updates on selected health services.

Objectives: We present a method for linking both data sources in the absence of non-unique identifiers.

Methods: MAX (at least 2-CF claims) and NCFR patients born between 01/01/1981 and 12/31/2006 were included. By combining various non-unique identifiers, we determined the percentage of uniqueness of records in each dataset. Only variable combinations with a 99% level of uniqueness were considered for defining the deterministic rules. A total of nine linkage rules were considered. We examined the linking performance of each rule as the proportion linked one-to-one to the registry and ascertained the validation parameters of these rules in the context of a selected gold standard (i.e., rule with the highest linkage performance).

Results: We assessed 14,515 and 15,446 patient records in MAX and NCFR datasets respectively. Linkage rule performance ranged from 1.4% (95% CI: 1.2–1.6) to 32.0% (95% CI: 31.3–32.8). As expected rules with lower linkage performance had fewer or no duplicate records. Using the selected gold standard, sensitivity of the other rules ranged from 4.3% (95% CI: 3.8–4.9) to 73.7% (95% CI: 72.0–74.6) with specificity of 85.2% (95% CI: 87.6–88.9) to 99.9% (95% CI: 99.8–99.9); the positive predictive value (PPV) ranged from 68.0% (95% CI: 62.6–73.4) to 99.0% (95% CI: 96.5–99.8).

Conclusions: The defined linkage rules exhibited varying operational characteristics and suggest that relying on multiple linkage rules may be necessary to optimize linkage performance.

857. Positive Predictive Value of Diagnosis Codes for "Anemia Caused by Bleeding" in the Danish Registry of Patients

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Background: Anemia affects nearly two billion people all over the world and is defined by haemoglobin levels below specific threshold values. It may be caused by acute or chronic bleeding. Readily available and accurate data are prerequisites to studies of occurrence and prognosis of this disease with high morbidity and mortality. The Danish National Registry of Patients (DNRP) covering all hospitals in Denmark may be used for these purposes, but the accuracy of the diagnostic coding of anemia caused by bleeding is unknown.

Objectives: To estimate the accuracy of diagnostic coding of anemia caused by bleeding in the DNRP using the clinical laboratory information system (Labka) as the reference standard.

Methods: We identified patients diagnosed with anemia caused by acute and chronic bleeding in the DNRP, in the period 2000–2009 (ICD-10 codes D50.0 or D62.9). We restricted to three hospitals in Denmark with available Labka data (Aarhus, Aalborg and Randers) and excluded patients younger than 18 years at diagnosis. For each hospitalization recorded in DNRP, all blood samples drawn between 30 days prior to admission and discharge date were scrutinized for lowest haemoglobin level using Labka data. We defined anemia in Labka as haemoglobin levels below 7 mmol/L for women and 8 mmol/L for men and estimated the positive predictive value (PPV) as measure of accuracy.

Results: In the DNRP, 3,391 patients were diagnosed with anemia. Of these, 3,234 had a low haemoglobin level in Labka, 115 had normal levels, and 42 had no records in Labka in the specified period, corresponding to an overall PPV of 3234/3391 = 95.4% (95% confidence interval (CI) 94.6–96.0%). The PPV was 97.6% (95% CI 96.6–98.3%) for men and 94.0% (95% CI 92.9–94.9%) for women and did not change by age at diagnosis. The PPV at gynecology departments was 89.2% (95% CI 83.4–93.4%), whereas surgery and medical departments had PPVs. similar to the overall results. For inpatients the PPV was 97.5% (95% CI 96.7–98.1%) and for outpatients 88.6% (95% CI 86.3–90.6%).

Conclusions: The diagnostic coding in the DNRP for anemia caused by bleeding had high accuracy.

858. Validity of Myocardial Infarction and Stroke Diagnosis Codes in a Managed Care Organization Database

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Background: As part of a post-marketing vaccine (V) safety study, possible acute myocardial infarction (AMI) and stroke events were carefully reviewed.

Objectives: To describe the validity of diagnosis codes of AMI and stroke used in the emergency department (ED) and hospital setting in a managed care organization.

Methods: Health outcomes requiring an ED visit or hospitalization within 42 days of vaccination (risk period) or a 90-day post-vaccination self-comparison period were analyzed in ˜29,000 vaccinated subjects 60 years of age or older as part of the study. Diagnosis codes listed for the health care encounters were grouped using the Healthcare Cost and Utilization Project (HCUP) hierarchical classification of ICD-9 codes. Electronic medical records of potential AMI (HCUP 7.2.3) and stroke (HCUP 7.3) cases in the risk or comparison periods were first screened to assess whether any acute event occurred for this health care encounter. Cases corresponding to planned or follow-up health care were excluded. All other cases were reviewed independently by two adjudicator specialists (cardiologists or neurologists respectively) to determine the event diagnosis and onset date, blinded to vaccination

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date, according to a pre-specified procedure. A third specialist acted as a tie-breaker when consensus was not achieved by the two adjudicators.

Results: Among the 29,010 study subjects, there were 97 records with an AMI code in the risk or comparison periods, of which 36 (37%) did not have an acute event, four had insufficient information for adjudication and 40 (41%) were confirmed as AMI. Of the 193 records with a stroke code, 116 (60%) did not have an acute event, two had insufficient data and 38 (20%) were confirmed as stroke.

Conclusions: Medical record review with adjudication of diagnosis resulted in confirmation of only 41% of potential AMI events and 20% of potential stroke events. Rigorous adjudication procedures are important to improve the validity of event diagnosis in database studies.

859. An Audit of the Diagnostic Coding of Pancreatitis of 331 Patients in Tayside, Scotland

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Background: The validity of diagnostic codes in observational research is of crucial importance. Incorrect diagnoses can mislead pharmacoepidemiological research outcomes in either direction.

Objectives: To validate the diagnosis of acute pancreatitis identified from the medicines monitoring unit (MEMO) database in Tayside, Scotland using a composite of hospitalisation codes or an occurrence in biochemistry database of a serum amylase >300 unit/L. With abdominal pain or abdominal pathology.

Methods: Two medical qualified doctors reviewed the medical notes of 331 idiopathic acute pancreatitis patients between 1993 and 2007. The clinical diagnosis criteria were (a) a hospitalisation for pancreatitis; or (b) serum amylase >300 unit/L with abdominal pain or abdominal pathology.

Results: Of 331 patients, 60 (18.1%) medical notes were destroyed. Two hundred and seventy-one (81.9%) medical notes were reviewed. Among 271 patients, 224 (82.7%) patients had a validated diagnosis, 11 (4%) patients had an invalid diagnosis and 36 (13.3%) patients had incomplete medical records. The accuracy of the diagnosis was 82.7% overall and 95.3% among those with complete medical records.

Conclusions: The definition of acute pancreatitis in the MEMO database was largely valid.

860. Validation of Claims Record on Acute Ischemic Stroke in the National Health Insurance Research Database Using Taiwan Stroke Registry as Reference

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Background: Although the National Health Insurance Research Database (NHIRD) has been commonly used to study acute ischemic stroke (AIS), the validity of diagnosis records remains unknown. The Taiwan Stroke Registry (TSR) database is a well-validated national database, representing 18% of all acute stroke admissions in 2006–2008.

Objectives: This study evaluated the validity of the AIS diagnosis in NHIRD using TSR database as reference.

Methods: This validation study used data from a single medical center participating TSR in 2006–2008. Patients with AIS diagnoses were identified from the registry data as the reference. Patients who had ICD-9 code (International Disease Classification code, 9th version) 433.xx or 434.xx in any of their five discharge diagnoses or only principal discharge diagnosis were identified from the NHIRD. We matched the two groups of patients using birth date, admission date, and discharge date to check the sensitivity, specificity, positive- and negative-predictive value (PPV and NPV). Cohen's Kappa with 95% CI (confidence interval) was calculated to check the diagnosis agreement.

Results: Using discharge diagnosis code of 433.xx or 434.xx in any of their five discharge diagnoses, the sensitivity, specificity, PPV and NPV were 81.6%, 99.9%, 67.0%, and 99.9%, respectively. The Cohen's Kappa was 0.74 (95% CI: 0.71–0.75). When restricting principle diagnosis code 433.xx or 434.xx, the sensitivity, specificity, PPV and NPV were 77.2%, 99.9%, 78.2%, and 99.9%, respectively. The Cohen's Kappa was 0.78 (95% CI: 0.76–0.79).

Conclusions: The accuracy of NHIRD in recording AIS admission was acceptable. The PPV of AIS diagnosis in NHIRD increased if we identified patients using only principle discharge diagnosis.

861. An Algorithm Using Free-Text To Identify Sudden Cardiac Death in the General Practice Research Database

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Background: Publications have shown that sudden cardiac death (SCD) is a challenging endpoint to identify in health claims data and electronic medical records (EMRs) due to the scarcity of specific data provided.

Objectives: To discuss the methods and limitations of using free-text data to identify SCD cases in the General Practice Research Database (GPRD).

Methods: GPRD was used to identify cases of SCD between January 2006 and January 2011. Potential cases were evaluated by investigating text associated with clinical and referral records for patients ±3 weeks from the recorded death date. Each text field up to a maximum of 500 characters was searched using pre-identified text strings related to SCD. Free-text of all potential cases was independently reviewed by two clinical experts. Positively adjudicated cases of SCD had to meet at least one of the following pre-specified criteria for both adjudicators: (1) pre-specified text string (''sudden death'', ''unexpected death'' or ''died suddenly''); (2) patient was found dead and no additional information on recent health status was available; (3) SCD specified; (4) fatal outcome preceded by a documented life-threatening ventricular arrhythmia; (5) cardiac death related reason in a patient without long term history of cardiac issues; (6) death directly related to a documented acute myocardial infarction. Cases with a hospitalization within the previous 30 days were not adjudicated as SCD.

Results: The analyses of outcomes were based on General Practices with an above average use of free-text per patient in each visit (40% of GPRD). A total of 996 potential cases were reviewed. Of 80% of the cases were adjudicated as potential SCD cases using only free-text. When free-text data was available, sufficient detail to make a definitive determination of SCD was often absent.

Conclusions: EMRs lack sufficient details for many patients in order to identify true cases of SCD. Although free-text data may help in the identification/rule-out of SCD, the limited amount of information for many patients restricts the ability of free-text data to adequately supplement EMR data to identify SCD.

862. Comparison of Various Strategies for Source Data Verification on Quality of Results in Observational Studies: A Simulation

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Background: One hundred percent (100%) source data verification (SDV) is generally the rule in clinical trials conducted by industry for regulatory and other purposes, despite the fact that there is no evidence to date that a reduced level of SDV necessarily results in compromised data quality. Observational studies, on the other hand, have been conducted with varying degrees of SDV with little known regarding the effect of SDV methods on the quality of the data and results so obtained. There are currently no guidelines addressing the appropriate SDV percentage in the observational study setting.

Objectives: The goal of this study is to qualitatively and quantitatively evaluate the effect of various SDV strategies on the quality of study data overall as well as study results. This was done using computer- simulated study samples into which varying degrees and types of data errors were introduced.

Methods: We will create simulated study samples using SAS 9.1 to reflect various study designs commonly used in industry sponsored late phase observational studies. To simulate the different types of error patterns which might occur, we will introduce errors into the samples. For each simulated sample/error pattern we will determine the effectiveness of reduced and modified SDV to identify those errors. In addition, we will run several analyses to measure the effect of various SDV strategies on summary statistics or results.

Results: We anticipate a better understanding of the effects of alternative strategies for reduced SDV in observational studies which would enable more cost-efficient study design and execution. This will allow for lower study costs while maintaining high study quality.

Conclusions: The cost-savings associated with reduced SDV could serve as an incentive for industry to conduct more observational studies with the confidence that the quality of the results is not negatively impacted when reduced SDV methods are employed. This may also provide a level of comfort to other consumers (providers and patients) of the study results.

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863. The Current State of Validation of Administrative Healthcare Databases in Italy: A Systematic Review

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Background: Health care databases assembled for administrative purposes are widely present at local and regional level in Italy. However, their validity for research purposes is unknown.

Objectives: To determine the number of administrative healthcare databases that have been validated in Italy; the type and number of diagnoses according to the International Classification Disease (ICD) that were validated; the frequency of use of each validated ICD codes for pharmacoepidemiological, epidemiologic and health services research; and the quality of reporting of the published studies.

Methods: A systematic review of electronic databases including Medline, Embase, Web of Science, Google (up to December 2011); Italian websites of healthcare services at national, regional and local levels; reference list of retrieved articles. Included studies used:

healthcare databases in any Italian territory routinely and passively collecting data without an a priori research question; the presence of health outcome, medical investigation or procedure at a patient level data; the use of a validation process. No language restriction was used. Studies using databases that were not truly administrative (e.g., cancer registries, epidemiology surveillance etc.) were excluded. Two pair of authors reviewed the articles for inclusion. Study citations were searched (via Scopus) to explore further use of the validation for research purposes. Quality of reporting was measured using appropriate checklist (Benchimol, *J Clin Epidem* 2011).

Results: A total of 7,214 references were evaluated, resulting in 178 publications. The studies were from national (n = 23), regional (n = 81), local (n = 16), hospital (n = 58) setting and covered 205 diagnosis using the ICD-9 or ICD-10 codes. Only five databases validated the following diagnoses: gastrointestinal perforation and bleeding, stroke, diabetes, amyotrophic lateral sclerosis.

Conclusions: Despite the widespread presence of administrative databases in Italy very few codes were validated. Administrative databases in Italy need extensive process of validation of multiple diagnoses codes to perform high quality pharmacoepidemiological and therapeutic risk management research.

864. Efficient Source Data Verification in Non-Interventional Studies: Literature Review of Current Methods

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Background: Drug research and surveillance after approval becomes more and more important. Non-interventional studies are effective in studying safety and effectiveness in "real life settings". Lack of specific regulatory requirements for source data verification (SDV) leaves sponsors to determine the method and level of SDV to ensure quality. It is more a company's decision to decide whether to do 100% SDV for all patients or to do 100% SDV of key data or otherwise.

Objectives: A literature review was performed to determine the current methods of SDV in published observational studies.

Methods: Google Scholar and Pubmed searches were used to retrieve relevant publications. The term "source data verification" was used in combination with the terms "observational study" and "non-interventional study". Articles readily available in full text were included for analysis. The methods sections were screened to determine the level of SDV applied. If multiple publications referred to a single study or registry, only one representative publication was selected for inclusion.

Results: Of the observational studies detected, 21 studies elaborated briefly on the way SDV was performed in their study. No SDV was performed in five studies, the remaining 16 studies performed 100% SDV on a percentage of the patients (median 10%). Generally, studies larger than 1,000 subjects sought to verify data sources for up to 10% of their population. One of these sixteen studies additionally performed SDV on a number of critical data points.

Conclusions: The way SDV is performed in non-interventional studies is not routinely specified in the methods section of publications. In those publications that did elaborate on study quality, the level of SDV ranges between 0% and 100%, with large (n > 1,000 subjects) observational studies restricting the level of SDV to a maximum of 10%. The investigators rather preferred to perform 100% SDV for all data for a certain percentage of patients then do 100% SDV of certain key variables only.

865. The Use of Gastrointestinal Protection for NSAID and Low-ASA Users: A Longitudinal Quality Study of Continuation across Hospitalisation

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Background: An increasing proportion of patients with incident peptic ulcer in Denmark, have been reported to be users of NSAIDs. It seems that the constant incidence of uncomplicated peptic ulcer can be a result of the increasing use of NSAID and ASA without concurrent use of gastrointestinal protection (GI protection).

Objectives: This study evaluates appropriate use of GI protection during NSAID and low doses of ASA (LowASA) treatment according to the recommendations in an elderly (+75) hospitalised population. It is a pilot study for a comprehensive register study of continued care across hospitalisation.

Methods: We preformed three cross-sectional analyses: before, during and after hospitalisation at Odense University Hospital linking a prescription register in primary care and hospital electronic medical records. The prevalence of proton pump inhibitors and H2-receptor antagonists was used as a measurement for appropriate GI protection. The hospital physicians' prescriptions of new initiated NSAID and LowASA treatments during hospitalisation were similarly analysed analysed according to concomitant risk factors.

Results: Sixty-two users of NSAIDs and 376 users of LowASA were included. In total, 17% and 54%, respectively, were admitted with suboptimal GI protection and without any changes during the hospitalisation. At admission, the prevalence of patients using no GI protection was 24% and 16%, respectively. Of these, 69% of NSAID users discontinued the use of NSAIDs, and 13.4% continued with addition of GI protection during hospitalisation. For patients using LowASA, 54% discontinued and 26.4% continued with addition of GI protection during hospitalisation. In hospital, there were 18% and 32%, respectively, newly initiated prescribings of NSAIDs or LowASA without GI protection.

Conclusions: The adherence to the recommendations of GI protection during NSAID and LowASA treatment was low, for patients admitted to hospital. At hospitalisation, the physicians modify the treatment according to the recommendations, but when hospital physicians initiated new NSAID and LowASA treatment, the adherence to recommendation was equally low.

866. Inappropriate Use of Gastroprotective Agent for Non-Steroidal Anti-Inflammatory Drug Therapy: A Hospital Cross Sectional Study

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Background: NSAIDs and COX2 have been associated with an increased risk of upper GI complications, in particular when risk factors are present. It is recommended that gastroprotective agents (GPAs) (i.e., misoprostol, proton-pump inhibitors, or H2 receptor antagonists) be taken concomitantly to prevent upper GI complications. Patients with Osteoarthritis and Rheumatoid Arthritis required long-term treatment with NSAID, however, an inappropriate (overuse/underuse) prescription of GPAs for these patients has been reported.

Objectives: This study aimed to investigate the appropriateness of concomitant GPAs among long term users of NSAIDs/COX2 in hospital setting in Indonesia.

Methods: We analyzed data on age, sex and dispensed drugs from a general hospital prescribed drugs register on 2009–2010 in Yogyakarta, Indonesia. It was located 2,060 prescriptions containing at least one NSAID/COX2 for 1868 patients with Osteoarthritis and Rheumatoid Arthritis. The presence of risk factors for NSAID-related gastrointestinal event and the GPAs used were registered. GPAs was considered appropriate/inappropriate used according to the current guidelines.

Results: Co-prescribing of GPAs were used by 763 (42.4%) of NSAID/COX-2 users. GPAs use was higher in females than in males and decreased in older age groups in both sexes. Meloxicam, piroxicam, glucosaminoglycan, and natrium diclofenac were mostly used concomitantly with GPAs. An underuse of GPAs was observed in 54.4% of ≥65-year-old, whereas an overuse occurred in 40.4% of ≤65-year-old patients without any risk factor. Concomitant therapy with either steroids (odds ratio [OR]: 1.22) or anticoagulants (OR: 1.50), and history of GI events (OR: 1.75) were significant predictive factors of inappropriate gastro protection.

Conclusions: Appropriate concomitantly use of gastroprotective agents for long term NSAID users in patients with Osteoarthritis and Rheumatoid Arthritis needs to be promptly implemented, as its inappropriate use is noticeably increasing ethical and economic concerns.

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867. Does Medication Adherence Itself Confer Fracture Protection? An Investigation of the Healthy Adherer Effect in Observational Data

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Background: Prior studies have shown a relationship between bisphosphonate (BP) adherence and reduced fractures. The extent to which fracture-adherence analyses might be confounded by the healthy adherer effect in real-world settings is unclear.

Objectives: To quantify the association between high adherence to different medications and fracture risk.

Methods: Using national U.S. Medicare data from 2006 to 2009, we identified patients with a new clinical fracture at the hip, spine, humerus, or wrist. Among these individuals, we defined three mutually-exclusive cohorts who initiated various therapies within 9 months post-fracture: (1) oral BPs; (2) selective serotonin reuptake inhibitors (SSRI), or 3) angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or calcium channel blocker (ACE/ARB/CCB). These medications have hypothesized favorable, unfavorable, and neutral effects on fracture risk, respectively. Adherence was categorized as high (MPR ≥ 80%), low (MPR < 50%), or intermediate (MPR 50 to < 80%). Cox proportional hazards models evaluated the association between hip and major osteoporosis fracture (hip, spine, humerus, or wrist) and high (vs. low) adherence within each medication group.

Results: We identified new users of oral BPs (n = 2043), SSRIs (n = 2485), and ACE/ARB/CCB (n = 1804) who initiated these therapies after fracture. Within each cohort, ~50% of patients had ≥80% adherence 6 months after initiation. Crude rates and adjusted hazard ratios for hip and major fractures showed that high adherence with BPs decreased both hip (HR = 0.64, 95% CI 0.37–1.12) and major fracture risk (HR = 0.61, 0.44–0.83), high adherence with SSRIs increased hip (HR = 2.12, 1.31–3.44) and major fracture risk (HR = 1.45, 1.07–1.98), and high adherence with ACE/ARB/CCBs was neutral toward fracture risk (hip HR = 1.35, 0.67–2.77, major fracture HR = 1.10, 0.74–1.63).

Conclusions: This study did not find evidence that medication adherence itself conferred a fracture benefit. Observational research on osteoporosis medication adherence and fracture risk may not be confounded by the healthy adherer effect.

868. Patterns of Intravenous Vitamin D Use among Hemodialysis Patients in the United States

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Background: Injectable vitamin D agents are commonly used to manage secondary hyperparathyroidism (SHPT) in dialysis patients. SHPT has been associated with various adverse outcomes including abnormalities in bone metabolism and soft tissue and vascular calcification. Yet, there is a lack of research documenting the patterns of use of these agents.

Objectives: We sought to describe patterns and variations in the use of the vitamin D formulations calcitriol, paricalcitol, and doxercalciferol in hemodialysis patients.

Methods: We studied hemodialysis patients in the United States Renal Data System between January 1, 1999 and December 31, 2008 with Medicare as a primary payer. Annual percentages of patients treated with each type of formulation were tabulated by race, sex, and age at dialysis initiation. The geographical distribution of vitamin D dose per patient was mapped at the state level.

Results: The study population consisted of 225,022 patients in 1999 and 315,608 patients in 2008. Intravenous vitamin D use has increased sharply from 1999 to 2008 with 83.9% of patients treated with any vitamin D formulation in 2008. The use of calcitriol has declined since 1999, from 58.6% of patients in 1999 to 1.8% in 2008. As of 2008, paricalcitol is the most frequently administered formulation. In 2008, the average dose among black patients was 84% greater than among white patients, 136 μg vs. 73.6 μg. Higher doses of vitamin D are administered to patients in the southern region of the country.

Conclusions: Vitamin D use has increased and parallels the rise in use of paricalcitol and doxercalciferol. The growing dominance of paricalcitol in the market suggests that the window of opportunity may be closing to determine comparative effectiveness and safety of the vitamin D agents using contemporary data. Given the known pharmacologic differences in vitamin D formulations, future research should focus on whether the formulations differentially affect patient outcomes.

869. Adherence to Anti-Osteoporosis Therapy in an Italian Local Health Unit

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Background: Although effective drugs for treatment of osteoporosis are available, adherence to these medications is currently low, with relevant impact on health outcomes.

Objectives: To analyze the adherence to anti-osteoporosis drugs in a Local Health Unit (Northern Italy) and to assess the influence of patient-related and drug-related factors.

Methods: Observational, retrospective study. Data on prescriptions of anti-osteoporosis drugs (AOD) -years 2007–2008- were retrieved from the administrative database of the local Pharmaceutical Service. Adherence was described by compliance and persistence at one year. Compliance was measured as medication possession ratio (MPR); optimal compliance was MPR ≥80%. Persistence was quantified by the number of days covered until discontinuation of therapy; patients who stopped treatment for >30 days were considered non persistent. The impact of some anagraphic and clinical variables was estimated using multivariate logistic regression analyses.

Results: Out of 4,304 patients (87.9% women, mean age 71 years) with a first prescription of AOD in 2007, 63.6% of patients had suboptimal levels of compliance (MPR < 80%) and 78.4% were non persistent. In regression analyses, younger (<50 years) age was significantly associated to poor compliance and no persistence (Odds Ratio [CI 95%] for adherence <80%: 2.437 [1.600–3.712] women and 3.505 [1.145–10.729] men; hazard ratio [CI 95%] for no persistence: 1.645 [1.336–1.981] women and 1.596 [1.082–2.352] men) and older (>75 years) age in women (OR 1.207 [1.051–1.387]; HR 1.120 [1.040–1.207]). Daily regimen was associated to poor compliance in women (OR 4.296 [1.801–10.246] and to no persistence in both genders (HRs 1.882 [1.364–2.596] women; 1.878 [1.146–3.078] men) vs. weekly regimen.

Conclusions: In our study, measurements of compliance and persistence identified 63% of subjects with discontinuous treatment and insufficient drug supply. Age and frequency of administration were strongly associated with adherence. These findings support the need for health intervention strategies to improve the performance of patients on therapy.

870. Prescribing of Strong Opioid Analgesics by UK Primary Care Physicians from 2000 to 2010

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Background: An increasing trend in opioid prescribing over the past 10 years has been reported, and this trend was associated with increasing incidences of dependence and misuse, healthcare resources consumption and death rate in the United States. However, little is known about the opioids prescribing in primary care settings in the United Kingdom (UK).

Objectives: This study evaluated the utilisation trends of strong opioid analgesics prescribed for pain management in the UK primary care settings.

Methods: This cross-sectional study was conducted from 2000 to 2010 using the General Practice Research Database, which is a large computerized health care database collected from 639 primary care practices throughout the UK. Prescribing data of patients who were prescribed strong opioid-containing drugs (buprenorphine, fentanyl, morphine and oxycodone) for pain management were extracted by using specific product codes. Total number of prescriptions for each drug was calculated. Descriptive statistics and simple linear regression were used to evaluate the proportion and annual trend of number of prescriptions.

Results: A total of 2.77 million prescriptions were identified for study drugs over the 11 years study period. Of those prescriptions, morphine was the most frequently prescribed category (n = 1.39 million, 50%), followed by fentanyl (n = 487,771, 18%), buprenorphine (n = 474,869, 17%) and oxycodone (n = 424,126, 15%). The trends of prescribing for all study drugs significantly increased ($p < 0.001$) from 2000 to 2010. Prescribing of oxycodone increased the most (10,960%) compared with buprenorphine (1,707%), fentanyl (1,135%) and morphine (394%).

Conclusions: This preliminary study showed that the prescribing trend for strong opioid analgesics in the UK has increased significantly in the past 11 years. Further studies are required to understand the reasons for the increasing prescribing trend, quantify the opioid prescribing doses and test the association between increasing opioid utilisation and clinical outcomes.

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871. Profile of Use of Anti-Tumor Necrosis Factor (anti-TNF) Agents in Rheumatoid Arthritis Patients in a Brazilian Healthcare Database, 2008–2010

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Background: Anti-TNF drugs have been increasingly used in patients with rheumatoid arthritis (RA) and were recently included in the list of medications eligible for governmental reimbursement in Brazil.

Objectives: To describe the pattern of use of anti-TNF drugs among RA patients in Minas Gerais state, Brazil.

Methods: APAC/SIA, a national administrative database that provides information on high cost procedures covered by the Brazilian National Health System, was used to identify a cohort of new users of Anti-TNF agents. Probabilistic record linkage was used to match registers prescriptions issued to the same patient. New users were defined as individuals aged over 18 years who had a first pharmacy claim for a prescription of a anti-TNF drug (adalimumab, infliximab or etanercept) with a index date within the period from January 2008 through December 2010, and who had not been prescribed with any anti-TNF drug during the 6 months prior to the index date. Social and demographic characteristics of patients, costs and the frequency of anti-TNF agent dispensed were analyzed.

Results: Among the population enrolled in the database from 2008 to 2010, a total of 5,668 individuals (6.6%) were identified as RA patients and 1,389 as new users of anti-TNF (1.6% of all patients and 24.5% of RA patients). Over 75% of these users (1,058) were female and mean age at first prescription was 50.2 ± 12.9 years. Most of patients (49%) were entered in the cohort in the year of 2010. Adalimumab was the most common drug prescribed (51.3%). Overall cost of treatment with anti-TNF was US$ 2.6 million in 2008 and US$ 3.8 million in 2010, an increase of 46%.

Conclusions: Probabilistic record linkage method was effective for linkage of APAC/SIA data. The linked database offers a longitudinal perspective of RA patients under anti-TNF treatment and creates a powerful resource to explore safety and cost-effectiveness of these new RA therapies.

872. Missing Data in Questionnaire Based Studies-Methodological Challenges and Success of a Regression-Based Imputation Model

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Background: In observational safety research, selection bias can occur if pts are excluded because of missing data. Methods of dealing with missing values include estimation (imputation) and sensitivity analysis.

Objectives: To explore a regression-based imputation method for dealing with missing data in a Prescription-Event-Monitoring (PEM) study of Bonviva (Ibandronic acid).

Methods: Exposure data were collected via prescriptions (Rx) issued by GPs between November 05-November 2007. Outcome data were collected via forms sent at least 6 months after 1st Rx. Pack size (1 or 3 tablets) requested to determine exposure period. Of 11,034 forms rtnd, pack size missing for 2,746 (24.9%). Completed forms revealed possible association between non-missing data (e.g., age) and pack size. Based on this, a regression-based imputation model was developed. Data were assumed to be missing at random, implying probability of missing outcome Y not dependent on Y after controlling for observed X covariates. Single random imputation used to estimate missing values. A single random logistic regression model with pack size as binary outcome was fitted with the covariates from pt and event data as predictors. Interaction between age and sex included in the fit. The model was trained on the non-missing outcome data and imputed for pts with missing pack size.

Results: Results indicated several covariates were significantly associated with pack size including age, sex, history of dyspepsia, bisphosphonates, oral steroid and anticoagulants. Imputations suggested that of 2,746 patients with missing data, 1,750 (63.7%) were prescribed 1 pack; 996 (36.3%) were prescribed three pack. These findings were consistent with manufacturer (Roche) sales data and NHS Rx Services Prescribing Analysis and Cost data.

Conclusions: Missing data on exposure can lead to inappropriately calculated exposure windows resulting in biased effect estimates. The single random imputation approach allowed pack size to be imputed for individual pts based on their non-missing pt-specific information. This method allows exposure periods for pts with missing information to be estimated and treatment periods for the entire cohort to be calculated.

873. Does the Dosing Regimen Affect Refill Adherence for Bisphosphonates?

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Background: Oral bisphosphonates are not as effective in reducing the risk of osteoporotic fractures as they could be due to low adherence rates. One reason for low adherence is the complex dosing regimens for bisphosphonates which could interfere with daily life.

Objectives: To examine differences in refill adherence and persistence between daily and weekly dosing of bisphosphonates using Continuous measure of Medication Acquisition (CMA) and the Maximum gap methods with focus on sensitivity to definitions.

Methods: Individuals aged 18–85 years who filled a bisphosphonate prescription between 1 July 2006 and 30 June 2007 and who had not purchased bisphosphonates in the prior year were followed until date of emigration, death, end of treatment or until 2 years after their index date. The data was collected by linkage between the Swedish Prescribed Drug Register, the National Patient Register and the Total Population Register. Number of days' supply was estimated based on instructions from the prescriber by developing an algorithm, which was validated by all authors in equal parts. Based on the dose regimen the patients were divided in two groups: 1 tablet daily and 1 tablet weekly. Analyses on refill adherence and persistence are currently in progress. Persistence is defined as the number of days from the first prescription until the end of duration of the last prescription with a grace period of 90 days. Refill adherence is estimated with the CMA (cut-off ≥80%) and the maximum gap method (cut-off 45 days). The impact of altering definitions, e.g., hospitalization, length of the observation period, and accumulation of medicines, will be analyzed.

Results: The study included 13,433 incident bisphosphonate users. Preliminary results show that 92% (12,311 patients) of these patients were using one tablet per week and 3% (371 patients) one tablet per day. The group using one tablet per week consisted of 1,871 men and 10,440 women, with a mean age of 69 years. The patients using one tablet per day consisted of 58 men and 313 women, with a mean age of 66 years.

Conclusions: In Sweden, the majority of bisphophonate users are women. A dosage regimen of one tablet per week is more common than one tablet daily.

874. Methodological Considerations for Examining OTC NSAID Exposure and Its Effects on Health Outcomes Using EMR Database

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Background: It is challenging to examine the health effects of exposure to over the counter (OTC) medications, such as certain NSAIDs, due to the lack of reliable information on utilization of these products captured in electronic healthcare records databases (relative to prescription products). Identifying a data source with reliable information on OTC medications would be a valuable asset to pharmacoepidemiology.

Objectives: To evaluate if a large Electronic Medical Record (EMR) from MedMining can serve as an appropriate data source for evaluation of OTC NSAID exposure in patient populations expected to be using NSAIDs (GI bleed patients and chronic pain patients) and examine what methodological issues would need to be addressed.

Methods: A large Electronic Medical Record (EMR) database from MedMining was identified as a possible source of data to examine OTC NSAID exposure among GI bleed and chronic pain patients. Several key issues were identified and evaluated for successful leveraging of this database for OTC drug research questions.

Results: Researchers aimed to comprehensively capture NSAID use, as well as to accurately distinguish between OTC and Rx use. Multiple methods for capturing any NSAID use were evaluated, including physician directed orders, patient-reported use, as well as notation in medical charts. Multiple methods for distinguishing between OTC and Rx were also explored, including whether the physician wrote an Rx or OTC order, as well as according to the dose of the NSAID. Further, we evaluated the ability to capture duration of use utilizing available start and stop date information.

Conclusions: Researchers examined multiple methods of capturing NSAID use, and distinguishing OTC and Rx use in this EMR database. It appears that in utilizing these methods, this EMR database provides reliable information on OTC NSAID exposure when compared with the available literature regarding prevalence of use amongst GI bleed patients.

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875. Correlates of Acetaminophen-Containing Product Knowledge

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Background: Acetaminophen is contained in hundreds of OTC and Rx products; lack of knowledge of dosing instructions and which medicines contain acetaminophen can increase the risk of overuse and liver damage.

Objectives: Examine the relation of various factors such as attitudes about medications, label reading behavior, and medication use characteristics to product knowledge among acetaminophen users.

Methods: Adult subjects were enrolled from an internet panel in 2010, and recorded their medication use prospectively on a daily basis for 7 days. Acetaminophen products taken were identified from a comprehensive list. An exit survey elicited attitudes, label reading, knowledge of product ingredients and dosing directions, demographics, medical history, and the SF-12 questionnaire on health status. Because lack of accurate knowledge about any one product could be sufficient to increase the potential for excessive use, knowledge was considered "correct' only if correct for all products taken. Logistic regression assessed the contribution of multiple variables to knowledge about product use directions.

Results: Among 3,618 users, 53% correctly identified acetaminophen as an ingredient of all products they had used during the diary period; 49% knew the correct interval between doses. Knowledge of the maximum amount to take at one time and in one day was 90% and 65%, respectively. Twenty-two percent had correct knowledge of each of the four label directions. Knowing that their product(s) contained acetaminophen was more common in people who used one drug (63%) than in those taking >1 (36%) and in users of OTC single ingredient products compared to OTC combination products (72% vs. 40%). Knowledge was positively associated with better physical health, the attitudes that one should comply with OTC and Rx directions for use and know the ingredients of products used; inverse associations were observed with daily smoking, nonwhite race, and the attitude that one should make one's own decisions about medication use.

Conclusions: There is substantial room for improving users' knowledge about ingredients and proper dosing of acetaminophen products. Correlates of product knowledge provide clues for targeting education efforts to promote safe use.

876. Acetaminophen Use Patterns Associated with Label Deviations

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Background: Acetaminophen is an active ingredient in many OTC and Rx products used to treat pain. Some acetaminophen products are single ingredient (SI); others are combined with other active ingredients (CO). There is concern that users may not follow label directions and thereby be exposed to excess doses of acetaminophen.

Objectives: To determine associations between particular products and uses, and deviations from label directions regarding concomitant use of multiple acetaminophen products, redosing too soon, and exceeding the maximum 1-time dose.

Methods: Of 3,618 US adults from an on-line research panel completed medication diaries for 7 consecutive days in summer 2010, reporting 25,878 medication occasions. GEE analyses related particular products to label deviations. Rx products, lacking uniform instructions, were excluded from 1-time dose analyses and assumed a 4-hour dosing interval.

Results: A concomitantly taken product was more likely to be Rx (OR = 2.0, 1.5–2.6) or OTC CO (1.7, 1.3–2.1) than OTC SI. Use too soon was less likely in Rx vs. OTC SI (0.3, 0.2–0.8). Among OTC SI, 650 mg 8-hour extended release products were more likely to be redosed too soon (2.9, 1.9–4.6), particularly those whose name included arthritis vs. 8 hours (2.6, 1.5–4.4). The 1-time dose was more likely exceeded for OTC SI products than OTC CO products (2.4, 1.7–3.3). Concomitant use was more likely when treating cold/flu/sinus symptoms (1.7, 1.3–2.2); redosing too soon (1.4, 1.1–2.0) and exceeding the 1-time dose (2.1, 1.5–2.9) were more likely when treating pain.

Conclusions: Deviations from label instructions for acetaminophen products varied with products and symptoms. Concomitant use was more likely when OTC CO and/or Rx products were used and when treating cold symptoms. This suggests the need to reinforce current directions not to take multiple acetaminophen containing products, and perhaps better identification of products containing acetaminophen. Redosing too soon and exceeding the recommended dosage was more likely among OTC SI products. These findings can be used to inform interventions to reduce acetaminophen use that deviates from label directions.

877. Consumption of Anti-Osteoporosis Medications in Spain

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Background: Anti-osteoporosis medications are frequently prescribed in Spain Recently, changes in the criteria to diagnosis osteoporosis, in the pharmacological treatments available and in the knowledge of their safety have been produced and they could have induced changes in the consumption of these medications.

Objectives: The aim of this study was to analyze the temporal trends of consumption of anti-osteoporosis medications in Spain between 2000 and 2008 and the influence in the consumption induced by the information sheets about the safety of hormone replacement treatment and strontium ranelate published by the Spanish Agency of Medicines and Health Products.

Methods: Data of purchase of anti-osteoporosis medications from 2000 to 2008 were obtained from the ECOM database of the Spanish Ministry of Health, which contains the pharmacy sales data of medicinal products reimbursed by the Spanish National Health Service. Data of consumption of anti-osteoporosis medications were expressed as defined daily dose per 1,000 inhabitants per day to women aged 50 or more.

Results: During the period of study, the consumption of anti-osteoporosis medications showed a continuous increase. The greater rise was observed with bisphosphonates, particularly alendronate and risedronate in their weekly formulations. The consumption of strontium ranelate was small but continuously increased and the new information about their safety in 2007 showed no effect on its consumption. The use of hormone replacement treatment remained stable until 2003, and from then showed a continuous decrease until 2008. Raloxifene use increased from 2000 to 2004 and decreased thereafter, calcitonins use decreased uninterruptedly and teriparatide was infrequently used.

Conclusions: This study shows a marked change in the treatment of osteoporosis in Spain, which includes an important increase of anti-osteoporosis medications use, particularly of bisphosphonates and a decrease of hormone replacement treatment use secondary to the new information about their safety.

878. Is It Important To Focus on the Treatment of Osteoporosis in Both Genders?

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Background: It is estimated that 900 thousand people suffer from osteoporosis in Hungary above 50 years of age. This condition highly increases the risk of fractures of vertebra and hip-bone, which often lead to fatal consequences. Regarding osteoporosis, we mainly consider women, although the disease affects significant portion of men: about 300,000 males in Hungary.

Objectives: To analyze the differences in the prevalence of osteoporotic fractures (using hip-fractures as an indicator) among men and women in Hungary, and to compare the elements and differences of therapeutic protocols of osteoporosis.

Methods: Our crude data came from the database of Tables of basic data on Hungarian health care regarding the year 2008. We standardized data for gender and age.

Results: In 2008 the total number of hip-fractures was 18,100, from which 12,393 were women and 5,707 were men. The incidence of fractures shows enormous increase above 65 years of age: while between 65 and 69 years the rate of hip-fractures was similar in both genders (281/100,000 inhabitants in males and 279/100,000 inhabitants in women), above the age of 85, this rate was 3,184/100,000 inhabitants in the female, and 1,907 in the male population. Considering the national therapeutic protocol of primary osteoporosis (postmenopausal and senile), bisphosphonates are the first choice drugs in both gender, however female patients receive strontium ranelate if the bisphosphonate use is contraindicated, while males teriparatide is given.

Conclusions: Since not only a large portion of the female population is affected by osteoporosis, but also a huge portion of the males, the prevention of fractures should be highly important in both genders, for which the screening of the population at risk and the appropriate treatment could be a good manner.

879. Non-Steroidal Anti-Inflammatory Drugs and Colorectal Cancer Progression and Survival: A Systematic Review

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Background: Multiple sources of evidence have demonstrated a strong inverse association between non-steroidal anti-inflammatory drug (NSAIDs) use and colorectal can-

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cer (CRC) risk. It is unclear however if NSAID use is associated with improved prognosis for patients with CRC.

Objectives: To summarise the available evidence on the association between NSAID use and disease progression and survival among individuals with newly diagnosed CRC.

Methods: Using terms for CRC and NSAIDs, MEDLINE, EMBASE and Web of Science were searched up to June 2011 without language restriction for studies that used clinically relevant outcomes for CRC such as CRC mortality, progression-free survival (PFS), disease-free survival (DFS) and recurrence-free survival (RFS). Unadjusted results for NSAID use vs. non-use were combined using random effects meta-analysis.

Results: Twelve studies met the inclusion criteria, six randomised controlled trials (RCTs), five cohorts and one case–control. Sample sizes ranged from 35 to 2,434 and follow-up varied from 1 to 12 years. Observational studies of aspirin use after CRC diagnosis were associated with reduced CRC mortality (HR 0.71, 95% CI 0.83–0.95), overall mortality (HR 0.65, 95% CI 0.65–0.97), DFS (HR 0.89, 95% CI 0.59–1.35) and RFS (HR 0.45, 95% CI 0.21–0.97). No association was observed for prediagnostic aspirin use and CRC mortality when risk estimates from four observational studies were combined (OR 0.92, 95% CI 0.75–1.11). The six RCTs reported no significant differences in PFS, DFS, and RFS among patients assigned to NSAIDs (celecoxib/rofecoxib) and due to heterogeneity amongst these studies, a meta-analysis was inappropriate.

Conclusions: Although there is a strong inverse relationship between NSAID use and CRC risk, at present, there is insufficient evidence of a protective effect of post-diagnostic use of NSAIDs/aspirin against progression of colorectal cancer. Additional data from cohort studies and RCTs is required.

880. Exposure to Non Steroidal Anti-Inflammatory Drugs and Risk of Cervical Intraepithelial Neoplasia Grade III

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Background: Epidemiological studies have suggested that exposure to non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin is associated with a reduced risk of several cancers and pre-malignant lesions via the inhibition of cyclooxygenase-2 (COX-2). This chemopreventive potential may extend to cervical intraepithelial neoplasia (CIN) lesions which to date has not been studied.

Objectives: The aim of this study was to investigate the association between NSAID exposure and risk of CIN grade III.

Methods: A nested case–control study was conducted within the General Practice Research Database (GPRD). Cases (n = 4,594) were females diagnosed with primary CIN grade III between 1st January 1995 and 31st December 2010. Controls (n = 18,820) were matched to cases (at date of diagnosis) on year of birth, sex and general practice. Conditional logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between NSAID exposure and risk of CIN III.

Results: Primary analyses examining exposure to NSAIDS during the 5 years prior to the index date (excluding 1 year before) found no association between ever NSAID use and risk of CIN III: OR 1.03 (0.96–1.10). A similar null association was observed between the cumulative number of NSAID prescriptions received and risk of a diagnosis. Further analyses found no overall association between NSAID dose (highest users of NSAIDs OR 0.91 [0.81–1.03], non-aspirin NSAIDs OR 0.91 [0.81–1.03] or high-dose aspirin OR 0.90 [0.40–2.00]) and risk of CIN III and no dose dependent response.

Conclusions: This study found no association between use of any NSAID and risk of CIN III.

881. Use of Non-Steroidal Anti-Inflammatory Drugs and Heart Failure Risk in the Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS) Project

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Background: Little evidence is available on the Heart Failure (HF) risk associated with use of individual Non-Steroidal Anti-Inflammatory drugs (NSAIDs).

Objectives: Assess the HF risk associated with NSAIDs use.

Methods: Data is being retrieved from seven European databases (DBs) covering different study periods: IPCI and PHARMO (the Netherlands); SISR, OSSIFF and PEDIANET (Italy); GePaRD (Germany); THIN (UK).

A case–control study, nested in a NSAIDs new-users adult cohort (≥18 years), is being carried out in each DB using common harmonized definitions for HF and relevant comorbidities. The cases are all patients with an HF hospitalization during follow-up. The index date is defined as the date of the first HF hospitalization. HF cases are matched to up to 100 controls by sex, age, follow-up length and index date. Odds ratios (ORs) for current use (14 days before index date) of individual NSAIDs vs. past use (184 days before index date) of any NSAID are estimated by conditional logistic regression adjusting for individual characteristics, comorbidities and concomitant drugs use. Pooled NSAID-specific ORs are obtained by a random effects meta-analysis approach to account for the DBs heterogeneity.

Results: Preliminary analyses of currently available data from SISR, OSSIFF and GePaRD included 14 NSAIDs and 57,416 HF cases. Compared to past use, current use of some traditional NSAIDs increased HF risk: diclofenac (SISR, OR = 1.3, 95% CI:1.2–1.4; OSSIFF, 1.3, 1.2–1.4; GePaRD, 1.4,1.3–1.6; Pooled, 1.3, 1.3–1.4); piroxicam (SISR, 1.3, 1.2–1.4; OSSIFF, 1.3, 1.1–1.4; GePaRD, 1.6, 0.9–2.8; Pooled, 1.3, 1.2–1.4); ibuprofen (SISR, 1.3, 1.2–1.4; GePaRD, 1.4, 1.3–1.7; Pooled, 1.3, 1.2–1.5); nimesulide (SISR, 1.2, 1.2–1.3; OSSIFF, 1.2, 1.1–1.3; Pooled, 1.2, 1.2–1.3). Among COXIBs, rofecoxib (SISR, 1.5, 1.3–1.7; OSSIFF, 1.3, 1.2–1.4; Pooled: 1.4, 1.2–1.6) and etoricoxib (SISR, 1.4, 1.3–1.6; GePaRD, 1.9, 1.3–2.9; Pooled, 1.6, 1.2–2.1) use were associated with higher HF risks, but celecoxib use was not.

Conclusions: These preliminary results suggest that some traditional NSAIDs and COXIBs increase HF risk.

882. Laboratory Monitoring of Patients Treated with Antihypertensive Therapy and Newly Exposed to Non Steroidal Anti-Inflammatory Drugs

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Background: Drug Interactions between Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blocker (ARBs) or diuretics can lead to renal failure and hyperkalemia. Thus, monitoring of serum creatinine and potassium is recommended when a first dispensing of NSAID occur in patients treated with these antihypertensive drugs.

Objectives: To evaluate the proportion of patients treated with ACEI, ARB or diuretic and receiving a first dispensing of NSAID who had relevant serum creatinine and potassium laboratory monitoring.

Methods: We described the first dispensing of NSAID among 3,500 patients of a 4-year cohort (6,633 antihypertensive-treated patients recorded in the French Health Insurance Reimbursement Database). We analyzed serum creatinine and potassium laboratory monitoring within the 3 weeks after the first NSAID dispensing.

Results: General Practitioners prescribed the majority of NSAIDs (85.5%, 95% CI: 84.3–86.6). The more commonly prescribed NSAIDs were ibuprofen (20%), ketoprofen (15%), diclofenac (15%) and piroxicam (12%). Relevant serum creatinine and potassium monitoring was 10.7% (95% CI: 9.5–11.8) in patients treated by ACEIs, ARBs or diuretics. Overall, monitoring was more frequently performed to patients aged over 60, treated with digoxin or glucose lowering drugs, but not to patients treated with ACEI, ARB or diuretic. Monitoring was more frequent when NSAIDs' prescribers were cardiologists and anesthesiologists.

Conclusions: Monitoring of serum creatinine and potassium of patients treated with ACEI, ARB or diuretic and receiving a first NSAID dispensing remains insufficiently performed and need to be reinforced through specific interventions.

883. Risk of Upper GastroIntestinal Complications Associated with Use of Individual Non-Steroidal Anti-Inflammatory Drugs in the SOS Project

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Background: SOS (Safety Of non-Steroidal anti-inflammatory drugs) project aims to asses and compare the risk of cardiovascular and gastrointestinal events with use of individual Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) using a collaborative approach throughout Europe.

Objectives: To estimate the risk of upper gastrointestinal complications (UGIC) associated with use of individual NSAIDs.

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Methods: A matched nested case–control study in a new adult NSAID-users cohort was performed during 2000–2010. Data are collected from seven databases participating in the SOS project: IPCI and PHARMO (Netherlands), SISR, PEDIANET and OSSIFF (Italy), GePaRD (Germany) and THIN (UK), involving 32 million subjects. This preliminary analysis was based on currently available data from OSSIFF and SISR. Up to 100 controls per case, matched on database, sex, age and index date, were selected by risk set sampling. Demographic and lifestyle information, co-morbidities and concomitant drug use were considered as potential confounders. Past users, i.e., cohort members whose exposure period ended 184 or more days before the index date, were used as reference. Adjusted odds ratios (ORs) for current use (14 days before the index date) of individual NSAIDs and their 95% confidence intervals were estimated using conditional logistic regression.

Results: The data from the two Italian databases comprised 10,087 UGIC cases matched with 988,068 controls. Current use of NSAIDs increased risk of UGIC especially for those taking ketorolac and piroxicam (OR > 4). OR estimates were between 2 and 4 for ketoprofen, meloxicam, etoricoxib and diclofenac, and between 1 and 2 for celecoxib, nimesulide, ibuprofen and rofecoxib.

Conclusions: Current use of individual NSAID increases the risk of UGIC. Compared to past users, the risk can be six times higher, depending on the NSAID used. The SOS study will be able to provide risk estimates on many more individual NSAIDs than previously was possible in a disparate approach.

884. Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and the Risk of Advanced Prostate Cancer

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Background: There is growing evidence that NSAIDs could reduce the incidence of prostate cancer (PC), but it remains unclear whether NSAIDs could also reduce the aggressiveness of the disease once it occurs.

Objectives: To assess whether NSAID use is associated with worse PC stage or grade at diagnosis.

Methods: Design: A case–control study using data from Saskatchewan (Canada) Cancer Registry and Prescription Drug Plan augmented by a clinical chart audit. *Setting*: Population-based. All men (N = 9,007) aged ≥40 years diagnosed with PC between 1985 and 2000 in Saskatchewan were included. *Exposures*: Five classes of prescription NSAIDs.

Outcome measures: Having at diagnosis locally-invasive PC (Whitmore-Jewett stage C), metastatic PC (stage D) or poorly differentiated PC (Gleason score > 7). *Statistical analysis*: Logistic regression models adjusting for potential confounding by age, calendar year of diagnosis, screening and, when appropriate, for use of other classes of NSAIDs.

Results: At diagnosis, 12% of cases stage C and another 15% had stage D disease. GS was >7 in 14% of cases. Any use of propionates (e.g., ibuprofen, naproxen) was inversely associated with the risk of both metastatic PC (OR = 0.81 [95% CI 0.71–0.93]) and advanced PC, OR = 0.86 (95% CI 0.77–0.95). Similar results were observed for arylacetic acids and oxicams and for aspirin. The control group in these analyses was PC patients with stage A and B. Any use of NSAIDs was inversely associated with the detection of poorly differentiated PC. However, the differences were statistically significant only for aspirin (OR = 0.84 [95% CI 0.72–0.97]) and for propionates (OR = 0.85 [95% CI 0.73–0.99]). The control group in these analyses was PC patients with GS <5 at diagnosis.

Conclusions: Our findings suggest modest benefits of at least some NSAIDs in reducing progression of PC into more aggressive disease.

885. Risk Models for Predicting Stroke and Upper Gastrointestinal Complications in NSAID Users: The SOS Project

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Background: In the SOS (Safety Of non-Steroidal anti-inflammatory drugs) project we aim to assess and compare the risk of cardiovascular and gastrointestinal events of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) with the ultimate goal of providing decision models to clinicians and regulatory authorities.

Objectives: To develop risk models for stroke and upper gastrointestinal complications (UGIC) in new NSAIDs users.

Methods: Data were collected from three databases participating in the SOS project: SISR and OSSIFF (Italy), and GePaRD (Germany). Patients were included from the moment of a first NSAID prescription and followed for

maximum a period of 5 years till their first event or transferring out of the database. Models for the risk of either stroke or UGIC were separately developed with Poisson regression models including follow up intervals of 0–2 weeks, 2–4 weeks, 1–12 months, 1–2 years, and 2–5 years. Discriminative ability was evaluated by concordance statistics.

Results: The three databases encompassed 6 million new NSAID users, with almost 40 thousand stroke and 15,000 UGIC events. The preliminary data showed that age and gender were strong predictors for both outcomes, leading to risk models with c-statistics of 0.78 and 0.76 for stroke and for UGIC respectively. More extensive risk models that included a large set of well known risk factors had similar c-statistics (0.79 and 0.76 respectively).

Conclusions: Simple risk models may provide adequate discrimination between patients with and without the evaluated outcomes stroke or UGIC upon NSAID use. Such risk models may well serve as input for decision models on individual NSAID prescription.

886. Immediate and Delayed Impact of Oral Glucocorticoid Therapy on Risk of Serious Infection in Older Patients with Rheumatoid Arthritis: A Nested Case–Control Analysis

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Background: Glucocorticoid (GC) therapy is widely used to treat patients with rheumatoid arthritis (RA). Although effective, there are concerns about serious infection, a major cause of increased mortality in RA patients. It is unclear how the risk depends on treatment regimes. Previous studies had limitations, including that they used exposure models ignoring patterns of drug use varying with time.

Objectives: To explore the relationship of serious infection risk with current and prior oral GC therapy in elderly patients with RA.

Methods: A case–control analysis matched 1,947 serious infection cases to five controls (matched for sex, age and entry date in the cohort), selected from 16,207 RA patients aged ≥65 who were dispensed ≥1 disease-modifying antirheumatic drug between 1985 and 2003, in the administrative databases of RAMQ and MED-ÉCHO in Québec, Canada. Adjusted odds ratios for infection associated with different GC patterns were estimated using conventional models and a weighted cumulative dose (WCD) model.

Results: The WCD model predicted risks better than conventional models. Current and recent GC doses had highest impact on current risk. Doses taken up to 2.5 years ago were also associated with increased risk, albeit to a lesser extent. A current user of 5 mg prednisolone had a 30% (95% CI: 21%–45%), 46% (CI: 31%–65%) or 100% (CI: 69%–126%) increased risk of serious infection when used for the last 3 months, 6 months or 3 years, respectively, compared to a non-user. The risk associated with 5 mg prednisolone taken for the last 3 years was similar to that associated with 30 mg taken for the last month. Discontinuing a 2-year course of 10 mg prednisolone 6 months ago halved the risk compared to ongoing use.

Conclusions: GC therapy is associated with infection in older patients with RA. The WCD model provided more accurate risk estimates than conventional models. Current and recent doses have greatest impact on infection risk, but the cumulative impact of doses taken in the last 2–3 years still affects risk. Knowing how risk depends on pattern of GC use will contribute to an improved benefit/harm assessment.

887. Alendronate Use and the Risk of Esophageal Cancer in Taiwan

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Background: Bisphosphonate is the medication used most widely to treat osteoporosis. Recently, some analyses have examined the association between exposure to oral bisphosphonates and the risk of esophageal cancer, but they produced seemingly discrepant results.

Objectives: Using a national database to evaluate the risk between exposure to oral bisphosphonates and the esophageal cancer in osteoporosis females in Taiwan.

Methods: We used the population-based National Health Insurance (NHI) database in Taiwan to conduct a retrospective cohort study during the period from 2000 through 2008. The study population confined to the women who took alendronate or raloxifene initially from January, 2002 to September, 2004 and medication needed to be stably prescribed for 90 days. The measurements of clinical outcomes included esophageal cancer (ICD-9 code 150) within 4 years after stable medication use. Cox's pro-

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portional hazard model was used to analyze the risk of esophageal cancer development.

Results: We identified 14,513 women who had been prescribed either alendronate or raloxifene. The patients treated with alendronate were not at a higher risk of diagnosis esophageal cancer compared with the raloxifene group (hazard ratio [HR] = 0.79 [95% CI, 0.254–5.456]).

Conclusions: Although patients who took alendronate did not have a higher risk of esophageal cancer than raloxifene patients. However, when undertaking the bisphophonates treatment, doctors still need to pay attention to the oral condition of patients.

888. Alendronate Use and the Risk of Osteonecrosis of Jaw in Taiwan

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Background: Bisphosphonate is the medication used most widely to treat osteoporosis. However, one serious adverse effect, osteonecrosis of jaw (ONJ), has been widely observed in those patients who took bisphosphonates. For the reason that there is no specific ICD-9-CM code for ONJ, pharmacoepidemiology studies regarding the relationship between bisphosphonates and ONJ is needed to be examined.

Objectives: Using a national database to evaluate the risk of bisphosphonate related ONJ in osteoporosis females in Taiwan

Methods: We used the population-based National Health Insurance (NHI) database in Taiwan to conduct a retrospective cohort study during the period from 2000 through 2008. The study population confined to the women who took alendronate or raloxifene initially from January, 2001 to September, 2005 and medication needed to be stably prescribed for 90 days. The measurements of clinical outcomes included ONJ-diagnosis (ICD-9-CM diagnosis code 526.4, 526.5, 528.3, and 730.18) and sequestrectomy (NHI payment code: 92025B and 92026B) within 3 years after stable medication use. Cox's proportional hazard model was used to analyze the risk of ONJ development.

Results: We identified 23,158 women who had been prescribed either alendronate (n = 18,504) or raloxifene (n = 4,654). The patients treated with alendronate were at a higher risk of ONJ-diagnosis compared with the raloxifene group (hazard ratio [HR] = 1.336 [95% CI, 1.100–1.622]). For sequestrectomy, patients took alendronate also had a higher risk than raloxifene group (HR = 4.648 [95% CI, 1.120–19.291]).

Conclusions: Patients who took alendronate had a higher risk of ONJ than raloxifene patients, no matter from the perspective of having the diagnosis or performing sequestrectomy. When undertaking the bisphophonates treatment, doctors need to pay attention to the oral condition of patients.

889. Choice of the Denominator for Case-Population Studies: Event Rates for Registration for Liver Transplantation in Acute Liver Failure Associated with NSAIDs or Paracetamol in France in the SALT Study

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Background: One of the concerns in case-population studies is the definition of the relevant exposure.

Objectives: To evaluate and compare population event rates in France using different source of denominators for ALF leading to registration for transplantation in patients exposed to NSAID or paracetamol, as a sub-study to the main SALT study.

Methods: All ALF cases exposed to non-overdose NSAIDs or paracetamol within 30 days before initial symptoms were identified over 2005–2007 in the French liver transplant units. Population exposure was computed from IMS sales data and from national healthcare insurance system data, as number of Defined Daily Doses (DDD) sold, number of patient-years, or number of exposed patients for the whole population and for the population aged 18–70 years.

Results: Nine cases exposed to NSAID and 49 cases exposed to non-overdose paracetamol were identified. Three-year NSAID sales ranged from 0.04 billion DDD for niflumic acid to 0.50 billion DDD for ibuprofen, 2.5 billion DDD for all NSAIDs pooled; 3.5 billion DDD for paracetamol. Over 3 years, use of NSAIDs in DDD per patient ranged from 13.2 for niflumic acid, 19.2 for ibuprofen, to 44.0 for diclofenac or ketoprofen, 63.9 for all NSAIDs pooled, and 63 for paracetamol. Numbers of users ranged from 1.65 million for niflumic acid to 15.2 million for ibuprofen, 22.7 for all NSAIDs pooled, and 35.5 for paracetamol. ALF rates per billion DDD ranged from 0 to 25 per billion DDD for individual NSAID, 3.96 for all NSAIDs pooled, and 13.8 for paracetamol. Rates per patient exposed over 3 years ranged from 0.26 per million for ibuprofen to 0.44 for diclofenac, ketoprofen, nimesulide or all NSAIDs pooled, with no significant difference between the individual NSAID. Event rate for paracetamol was 1.38 per million patients, 3.24 (95% CI 1.59–6.19) times higher than all NSAID pooled.

Conclusions: Using number of users rather than DDD resulted in reduced variability between individual NSAIDs, but did not change the association of ALF resulting

in registration for transplantation with non-intoxication paracetamol.

890. Use of Bisphosphonates and Risk of Atypical Femur Fracture: A Systematic Review and Meta-Analysis

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Background: Bisphosphonates are the most commonly used drugs for the prevention and treatment of osteoporosis. Although there have been an increasing number of studies reporting a link between use of bisphosphonates and atypical femur fracture (AFF) in the subtrochanteric or diaphyseal region as a consequence of over-suppression of bone resorption, there is still limited data available.

Objectives: We aimed to conduct a systematic review and meta-analysis of published studies to evaluate risk of AFF associated with bisphosphonates use.

Methods: A comprehensive search in MEDLINE and EMBASE was performed using a combination of the Medical Subject Headings and keywords (January 1st, 1990 to December 26th, 2011). Our search was limited to English language articles. Case series or reports were excluded. We calculated pooled risk ratios (RR) using a random-effects model and examined between-study heterogeneity with the I-squared statistic.

Results: Eleven eligible studies including 2,203,178 patients were identified. One reported the results of secondary analyses of randomized clinical trials, plus 5 cohort and 5 case–control studies. Across all studies, bisphosphonate exposure was associated with an increased risk of AFF (pooled RR: 2.71; 95% CI: 1.42–5.21). Large heterogeneity was noted (I-squared = 92%). Stratified analyses by study design showed a RR (3.48, 95% CI 1.11–10.95) for case–control studies. Subgroup analysis of 6 studies including data regarding long-term use of bisphosphonates yielded a RR of 3.70 with a wide 95% CI (0.35–38.81). After limiting the analysis to 2 studies that confirmed the characteristics of AFF in the long-term users of bisphosphonates, the RR was 13.79 (95% CI 1.46–130.40).

Conclusions: Our study found an elevated risk of AFF associated with bisphosphonate exposure. A more pronounced risk was observed in long-term users of bisphosphonates and in studies that confirmed the type of fracture. Given the heterogeneity between the studies and the known benefit of bisphosphonates on osteoporosis, these results should be interpreted with caution but suggest that bisphosphonate use is associated with an increased risk of relatively rare femoral fractures.

891. Potentially Harmful Prescription of NSAIDs in a Primary Care Population with Musculoskeletal Complaints

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Background: General practitioners (GPs) frequently treat patients with musculoskeletal complaints (MSC) with nonsteroidal anti-inflammatory drugs (NSAIDs).

Objectives: To determine the extent of potentially harmful prescription of NSAIDs in a primary care population with MSC.

Methods: Data were retrieved from the Integrated Primary Care Information (IPCI) database, a longitudinal GP research database containing over one million patient records. All new episodes of MSC occurring in adult patients (> = 18 years) between 2000 and 2010 were identified based on the International Classification of Primary Care (ICPC)-coding. For all episodes, NSAID prescriptions issued on the day of a consultation were subsequently identified. NSAID prescriptions were considered potentially harmful if given to patients at a high risk of adverse drug events (ADEs), defined as a high renal risk (glomerular filtration rate < 30ml/min), high cardiovascular (CV) risk (history of ischaemic heart disease, stroke, peripheral arterial disease or heart failure), or high gastrointestinal (GI) risk (history of upper GI bleeding or ulceration, age > 70 years, or two or more of the following: age 60–70 years, history of heart failure, diabetes or severe rheumatoid arthritis, use of antithrombotics, corticosteroids, selective serotonin reuptake inhibitors or high dose NSAIDs, without adequate concomitant gastroprotection (either a selective cox-2 inhibitor or a nonselective NSAID with concomitant proton pump inhibitor, misoprostol or double dose histamine-2 receptor antagonist).

Results: In 24.6% of all 1,632,005 episodes of MSC which occurred, an NSAID was prescribed. Of all NSAID-prescriptions, 10.6% were considered potentially harmful to the renal, CV and/or GI tract. More specifically, 0.03% were prescribed to patients at high renal risk, 6.8% to patients at high CV risk and 8.9% without adequate gastroprotection to patients at high GI risk.

Conclusions: GPs routinely treat patients with MSC with NSAIDs and do not take the patients' risk profiles sufficiently into account in one tenth of prescriptions, particu-

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larly in patients at a high risk of serious gastro-intestinal ADEs.

892. Use of Bisphosphonates and the Risk of Osteonecrosis: A Systematic Review and Meta-Analysis of Observational Studies

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Background: Osteonecrosis (ON) is death of osteocytes following compromised blood circulation to the bone. Femoral head of hip is the most common sties for ON, but any site in bone with compromised blood or nutrient supply may develop ON. Osteonecrosis of the jaws (ONJ) is an extremely rare clinical entity. Since 2003, case reports and case-series of ONJ have emerged and these cases were linked to the use of bisphosphonate (BP) treatment in patients with cancer or osteoporosis. Several studies showed the strong association between the use of BPs and the risk of ONJ, but the magnitude of risk varied greatly between studies.

Objectives: To quatitatively summarize the association between use of bisphosphonate and by performing a systematic review and meta-analysis.

Methods: Two independent reviewers searched Medline and EMBASE, and screened articles for inclusion and exclusion criteria. Data and study quality were assessed according to published guidelines. Summary odds ratio and 95% confidence intervals (CI) were calculated with fixed or random-effects models depending on the heterogeneity of the included studies. Tests for heterogeneity and publication bias were performed.

Results: We identified 14 observational and three randomized controlled trials on use of BPs and risk of ON. Compared to those without use of BPs, Summary OR for use of BPs was 2.85 (95% CI 1.68, 4.85) for all included studies, 2.47 (95% CI 1.00, 6.18) for patients without cancer, 2.92 (95% CI 1.80, 4.74) for patients with cancer, and 3.61 (95% CI 1.70, 7.67) for patients with multiple myeloma. Intravenous BPs (OR: 8.75; 95% CI 4.82–15.90) were associated with higher risk for ONs than oral BPs (OR: 2.68; 95% CI 1.36–5.27). The association was stronger for ON of jaw (OR: 3.32; 95% CI 1.75–6.27) than ON of other sites (OR: 1.79; 95% CI 0.71–4.47). There are significant heterogeneity (I-squared > 50%) among most of the major and subgroup analysis.

Conclusions: Use of BPs, especially intravenous BPs, is associated with strong and significant risk for ON of Jaw. Appropriate preventive dental care and frequent dental exam is recommended for patients receiving BP therapy.

893. Abstract withdrawn by author.

894. Association of Serum Potassium and Arrhythmia in Patients Prescribed NSAIDs

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Background: NSAIDs are associated with arrhythmias but the mechanism by which this occurs is poorly understood. NSAID-associated increases in serum potassium could play a role.

Objectives: To determine the risk of arrhythmia in patients prescribed nonselective or COX-2 selective NSAIDs and ascertain the role of serum potassium.

Methods: We conducted a case–control study of patients prescribed NSAIDs between 2004 and 2009. Cases had evidence of arrhythmia and serum potassium results within the year prior to their index drug (baseline) and ±7 days of the arrhythmia in the database. Controls with baseline potassium were matched to cases by age (±5 years) and timing of serum potassium results post index drug exposure (±7 days). We used the Regenstrief Common Data Model containing electronic health records or administrative claims data in Indiana. Nonselective NSAIDs excluded aspirin and salicylates. Patients switching from one NSAID to another without a gap within each type were bridged in the same drug era. Of 298,113 patients were prescribed an NSAID (277,940 nonselective and 20,173 COX-2 selective). We searched for evidence of ventricular and supraventricular arrhythmias after first receipt of NSAID. Of the 298,113 patients exposed to NSAID, we identified 1,990 cases, 517 of whom had baseline and postexposure serum potassium concentrations. We used conditional logistic regression analysis controlling for renal impairment.

Results: The mean age of the 517 cases and controls was 60 years (±18 SD). Renal impairment was present in 27% of cases and 23% of controls. Nonselective NSAIDs were prescribed to 381 (74%) of cases and 458 (89%) of controls. COX-2 inhibitors were prescribed to 136 (26%) of cases and 59 (11%) of controls. The mean change in serum potassium from baseline was 0.4 (±1.1) for cases and -0.1 (±1.0) in controls. Compared to nonselective NSAIDs, the odds of arrhythmia in patients prescribed COX-2 inhibitors was 2.78 (95% CI, 1.90 –4.06) and the odds of change in serum potassium was 1.63 (95% CI, 1.38–1.91).

Conclusions: The risk of arrhythmia is greater for COX-2 inhibitors than nonselective NSAIDs and appears to be associated with increased serum potassium concentrations.

895. Etoricoxib in the UK: Continuing vs. New Users after the COX-2 Urgent Safety Restriction (USR)

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Background: Etoricoxib is indicated for the treatment of osteoarthritis (OA, 30–60 mg), rheumatoid arthritis (RA, 90 mg), ankylosing spondylitis (AS, 90 mg), and gout (G, 120 mg). The COX-2 USR highlighted CV risks with NSAIDs and recommended treatment with the lowest effective dose for the shortest possible time.

Objectives: To examine the baseline characteristics of, and use of etoricoxib in, continuing vs. first time users of etoricoxib after the USR.

Methods: We identified all patients in the UK GPRD database with ≥1 prescription (rx) for etoricoxib through 31 December 2009. We evaluated baseline factors (within 12 months prior to the initial rx) and treatment data in those who used etoricoxib both before and after the USR (continuing users) and those whose initial rx was after the USR (new users).

Results: There were 7,453 continuing users and 29,047 new users. Continuing users were more likely to have a labeled indication (76% vs. 59%) in their medical record and had higher mean baseline systolic BP (136 vs. 132 mmHg). Continuing users also had greater baseline history of edema (9.9% vs. 6.8%), subacute heart disease (9.3% vs. 7.6%), and hypertension (34.2% vs. 28.9%). Continuing users more often previously used other COX-2s (21.7% vs. 6.7%), paracetamol (56.2% vs. 46.1%), rheumatic disease modifying drugs (8% vs. 3.4%), and any GI drugs and CV drugs at baseline. A greater% of continuing users were prescribed 60 mg (50% vs. 46.1%) and 90 mg (34.3% vs. 28.2%) but a lower % of them were prescribed 30 mg and 120 mg. The median no. of days of treatment over 1 yr of follow-up for continuing users vs. new users, by indication, was OA 112 vs. 56, RA 224 vs. 70, AS 206 vs. 112, G 28 vs. 28, two or more of OA RA AS G 126 vs. 28, arthritis not specified 112 vs. 56, none of the above 60 vs. 28. Treatment duration was longer in continuing users regardless of gender, age, or dose.

Conclusions: After the COX-2 USR, continuing users of etoricoxib more likely had a labeled indication, used higher doses and were treated longer with etoricoxib than new users, perhaps due to differences in the severity of the disease under treatment.

896. Etoricoxib Prescribing by GPs in the UK after the COX-2 Urgent Safety Restriction (USR)

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Background: Etoricoxib is indicated for the treatment of osteoarthritis (OA, 30–60 mg), rheumatoid arthritis (RA, 90 mg), ankylosing spondylitis (AS, 90 mg), and gout (G, 120 mg). The COX-2 USR recommended treatment with the lowest effective dose for the shortest possible time.

Objectives: To examine prescribing of etoricoxib by GPs in the UK after the COX-2 USR of 18 February 2005.

Methods: We identified all patients in the UK GPRD database who had a first time prescription (rx) for etoricoxib issued on or after 18Feb2005 through 31Dec2009. In these patients we evaluated labeled indications for etoricoxib, and dose and duration of treatment over the course of 1 year of follow-up (f-u) following the initial rx.

Results: Of 29,047 pts received ≥1 rx for etoricoxib (mean new rxs/month 499). The% of patients with labeled indications were OA 32.0%, RA 3.2%, AS 1.0%, G 13.1%, two or more of OA RA AS G 4.8%, arthritis not specified 4.4%, and none of the above 41.5%. The most commonly prescribed doses (mg) for the first rx by indication were OA 60, RA 90, AS 90, G 120, two or more of OA RA AS G 60, arthritis not specified 60, none of the above 60. Doses by age <65 vs. ≥65 were 30 mg 6% vs. 9%, 60 mg 44% vs. 51%, 90 mg 31% vs. 23%, 120 mg 20% vs. 18%. The mean (median) no. of days of treatment over 1 year of f-u by indication were OA 102 (56), RA 138 (70), AS 160 (112), G 41 (28), two or more of OA RA AS G 96 (28), arthritis not specified 106 (56), none of the above 64 (28). The mean (range) no. of days of treatment over the entire study period for all indications combined was 150 (1–2139). Treatment duration was similar for men and women, and for those age <65 and ≥65; it was also similar for the 30, 60 and 90 mg dose, but shorter for the 120 mg dose. Over the entire study period, the% of patients who switched to a higher dose, lower dose, or another NSAID was 6.6%, 6.5% and 51%, respectively.

Conclusions: Of 41.5% of patients who were prescribed etoricoxib after the COX-2 USR did not have a labeled indication of OA, RA, AS, or gout in the medical record. Otherwise etoricoxib was generally prescribed according to labeling and the USR instructions to prescribers.

897. Incidence of Cardiovascular (CV) Events with Etoricoxib in the UK after the COX-2 Urgent Safety Restriction (USR)

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Background: Etoricoxib is indicated for the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. The COX-2 USR of 18Feb2005 highlighted

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CV risks with NSAIDs and recommended treatment with the lowest effective dose for the shortest possible time.

Objectives: To estimate the incidence of CV events with use of etoricoxib among general practice patients (pts) in the UK after the COX-2 USR.

Methods: We identified all pts in the UK GPRD database first prescribed (rx) etoricoxib on or after 18 February 2005 through 31 December 2009. Exposure to etoricoxib was defined current on any date within the calculated days supply from the most recent rx +14 days. The incidence of CV events (defined by READ codes) with current exposure was estimated over a 1-year period of follow-up after the initial rx.

Results: Of 29,047 pts first received etoricoxib during the study period (mean age 58 years, 57.4% women). Baseline CV risk factors included age ≥65 34.1%, current smoking 21.2%; obesity 28%; systolic BP ≥140 37.7% and diastolic BP ≥90 14.6%. Baseline medical history prevalence ranged from 1.0 to 7.6% for acute or subacute CV diagnoses and 28.9% for hypertension, 12.7% for dyslipidemia and 7.9% for diabetes diagnosis. The incidences (95% CI) per 1,000 patient-years for CV events were heart failure 4.0 (2.5, 6.0), acute myocardial infarction 2.5 (1.4, 4.1), unstable angina 0.4 (0, 1.3), hemorrhagic stroke 0.3 (0, 1.2), ischemic stroke 1.2 (0.5, 2.5), stroke not classified 2.4 (1.3, 4.1), transient ischemic attack 3.2 (1.9, 5), deep venous thrombosis 2.1 (1.1, 3.6), pulmonary embolism 4.1 (2.6, 6.1), sudden death 0.2 (0, 1), and any vascular or sudden death event (all of the above except heart failure) 12.8 (10, 16.3).

Conclusions: Patients prescribed etoricoxib after the COX-2 USR included a high proportion of patients with CV risk factors. The incidence of CV events with use of etoricoxib was low. The overall incidence of any vascular or sudden death event was 1.3%/year of exposure, which is in the expected range for the patient population with chronic indications for COX-2 inhibitors/NSAIDs.

898. Exploratory Analysis To Improve Identification of Early Users of Prolia® in a Claims Database

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Background: The assignment of specific procedure codes for a new drug commonly occurs months after marketing approval, requiring that early claims are coded with non-specific codes. This creates challenges in identifying from medical claims early users of the new drug. Distinct attributes of a new drug may be leveraged to improve capture of drug administrations. Prolia, indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, was approved in June 2010.

Objectives: To estimate the number of new users of Prolia from June to December 2010.

Methods: Using a US claims database, all claims with a non-specific Healthcare Common Procedure Coding System (HCPCS) procedure code for unclassified drugs or biologics among a population with postmenopausal osteoporosis (PMO) from June to December 2010 were identified. We tabulated the HCPCS by concomitant National Drug Code (NDC), total cost on claims (< $800, ≥$800), and source of claim to assess the proportion of all non-specific procedure codes that may be attributed to Prolia administrations.

Results: We identified 1,746 claims with the presence of a non-specific procedure code among the PMO population, of which 101 (6%) were associated with a cost equal to or > $800, and 71 (4%) had a concomitant NDC indicative of Prolia. There were 736 claims with a non-specific HCPCS that were not accompanied by a NDC; of these, 40 were associated with a cost of ≥$800. Assuming that the total cost for Prolia is at minimum $800, we can estimate that the upper bound of the number of potential Prolia claims that we may have missed by requiring a specific Prolia NDC is 40, for a total of 111 Prolia claims including the 71 Prolia claims identified by NDC codes.

Conclusions: Identifying early users of newly approved drugs is essential to fulfilling many post-marketing commitments. Taking into account the cost associated with claims likely improves capture of Prolia administrations, and allows for well-informed sensitivity analyses for exposure misclassification.

899. The SOS Project: Incidences of Reported Cardiovascular Events in RCTs

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Background: As part of the Safety Of non-Steroidal anti-inflammatory drugs (SOS) project funded by the European Commission, a systematic review of randomized clinical trials (RCTs) was performed to select the most relevant RCTs in terms of safety of NSAIDs.

Objectives: To calculate the incidence of myocardial infarction (MI), ischemic stroke (IS), hemorrhagic stroke (HS) and heart failure (HF) in NSAIDs users during RCTs.

Methods: Medline, Scopus, ISI web of Science, and Cochrane database of Systematic reviews were searched for RCTs published between 1983 and 2008 for the 10 most sold NSAIDs in Europe. RCTs with no treatment arm over 100 patients-years (P-Ys) were excluded. The incidence was expressed in incidence per 1,000 P-Ys.

Results: Among 1,222 potentially relevant references, 51 RCTs fulfilled inclusion criteria. For MI, celecoxib incidence was 5.5 per 1,000 P-Ys (95% CI, 4.2–6.8), diclofenac 4.4 (3.6–5.1), etoricoxib 4.2 (3.4–4.9), ibuprofen 2.8 (1.4–4.2), indomethacin 8.7 (0.2–48.2), meloxicam 0.0 (0.0–24.1), and naproxen 2.5 (1.6–3.4). For IS, celecoxib incidence was 1.9 per 1,000 P-Ys (95% CI, 0.5–4.8), diclofenac 2.1 (1.6–2.6), etoricoxib 2.0 (1.5–2.5), ibuprofen 2.1 (0.9–3.3), indomethacin 0.0 (0.0–31.9), meloxicam 0.0 (0.0–24.1), and naproxen 3.0 (1.6–4.4). For HS, celecoxib incidence was 2.0 per 1,000 P-Ys (95% CI, 1.1–3.0), diclofenac 0.7 (0.0–4.0), ibuprofen 0.5 (0.1–1.5), indomethacin 0 (0.0–31.9), meloxicam 0.0 (0.0–24.1), and naproxen 0.2 (0.0–1.1). For HF, celecoxib incidence was 2.7 per 1,000 P–Ys (95% CI, 1.8–3.6), diclofenac 2.4 (1.3–3.4), etoricoxib 0.6 (0.1–1.2), ibuprofen 4.2 (2.5–5.9), indomethacin 0 (0.0–31.9), meloxicam 0.0 (0.0–7.2), and naproxen 4.1 (2.7–5.5).

Conclusions: Potential differences in the incidence of the studied CV events were observed between the NSAIDs for which sufficent long term data from RCTs are available.

900. Incidence Rates (IR) of Events Related to Over-Suppression of Bone Turnover among Women with Postmenopausal Osteoporosis (PMO)

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Background: Concerns have been raised that long-term use of bisphosphonates (BP) and other osteoporosis (OP) medications may result in bone turnover over-suppression and increase risk of events such as osteonecrosis of the jaw (ONJ) and atypical femur fracture. However, the etiologically relevant time window following treatment initiation is unclear.

Objectives: To estimate among women with PMO, the IR of ONJ and nontraumatic subtrochanteric/diaphyseal fracture (NSDF), of which only a small fraction are truly atypical femur fracture, over various risk windows following exposure to BP and/or other OP medication.

Methods: Women ≥55 years with ≥6 months of data in the MarketScan claims database were included in a PMO cohort (N = 836,354) if they received a diagnosis or treatment related to OP between 01/2004 and 07/2010. Women were followed for ONJ and NSDF from cohort entry to the earliest of event occurrence, disenrollment or 07/2010. OP and outcomes were identified by ICD-9 codes and treatment by drug codes. Based on received BP or other OP medications, follow-up was classified as risk window periods defined by on-treatment (OT, days supplied + 30-days) or OT + 1 year post-treatment (PT). IR were estimated within these treatment-defined times at risk.

Results: Overall, the IR/100,000 p-yrs of ONJ and NSDF were 32.3 and 100.3, respectively, with no substantial variation across risk windows defined by treatment. For the risk window defined by OT and OT + PT, ONJ rates among p-yrs with BP only (33.8 and 34.5, respectively) and both BP and other OP medications (49.2 and 38.5, respectively) were slightly higher than those among untreated p-yrs (30.8 and 30.1, respectively). Relative to risk windows defined by OT + PT, NSDF rates during OT were slightly lower among p-yrs with BP only (99.1 vs. 104.6) and BP and other OP treatment (72.4 vs. 81.4).

Conclusions: We did not observe substantial variation in ONJ and NSDF rates assuming different risk windows following BP and other OP treatment. Future studies with case adjudication are needed to further evaluate the time at risk for these events following OP treatment.

901. Exploring the Use of an Adverse Event Detection Tool on Real Data: Temporal Relationship between Two Events and the Exposure to Oral Biphosphonates

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Background: Cornelius et al. have recently suggested a new signal detection tool for adverse event detection (WSP: Weibull Shape Parameter tool), which allows the detection of a temporal causal relationship between exposure and event. This tool, based on fitting a Weibull model on time to event data, has shown very good reliability on simulated data.

Objectives: To explore the performance of the WSP tool on real data: detecting a temporal relationship between the diagnostic of carpal tunnel syndrome and upper GI cancer in women exposure to oral biphosphonates.

Methods: Retrospective cohort study: The Health Improvement Network (THIN) database, United Kingdom.

Setting and exposure: Women > 51 years who received a prescription for an oral bisphosphonate between 1994 and 2006. Each woman is matched on age with two controls form same practice. Women with Pagets disease or cancer were excluded.

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Main outcome and statistical analysis: Applying the WSP tool on data for exposed and control separately consisted of censoring the data at regular intervals for a period of 3 years (carpal tunnel syndrome), 7 years (upper GI cancer) and fitting a Weibull model. If a shape parameter significantly different from the value one is obtained a signal is raised for further investigation.

Results: Observation of the time to event data for exposed and control groups showed that over the observation periods the smoothed empirical hazard functions are constant for both groups for each of the events. Applying the WSP tool on both groups with a censoring interval of 6 months did not result in any significant value for the shape parameter of the Weibull model, so for exposed and control groups no signal was raised.

Conclusions: Whilst previous work has provided evidence for an increased risk between carpal tunnel syndrome and upper GI cancer, there was no evidence that this relationship was temporal in nature with the WSP detection tool. Discussion points include possible interpretations for the observed difference in hazard rate (confounding factors) between the groups and also how the number of events will impact on the power may affect results.

902. A Survey of Patient Awareness and Use of Medicine Containing Acetaminophen

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Background: Acetaminophen is the most commonly used analgesic in part due to its inclusion in many over-the-counter (OTC) products and prescription opioids. While generally safe at recommended doses, supra-therapeutic doses (>4,000 mg/day) are associated with acute liver failure (ALF). Acetaminophen overdose is a leading cause of ALF in Western countries. A majority of unintentional overdoses are among users of acetaminophen containing opioids.

Objectives: To provide information on OTC and prescription acetaminophen use, use of supra-therapeutic doses, awareness of acetaminophen -related toxicity, and perceived effectiveness and preferred avenues for educational interventions across 3 distinct cohorts.

Methods: A survey of US health plan enrollees identified from automated pharmacy data who were long-term and acute users of opioids with acetaminophen (n = 720 each cohort) and a general population cohort (n = 360) during the 2010–2011 cold/flu season – 74% response rate. Differences were tested across the 3 cohorts, and by level of education, using age-adjusted regression models.

Results: Use of OTC or prescription medicine containing acetaminophen in the prior 2-weeks was reported by 84% in the long-term opioid cohort, 76% in the acute opioid cohort, and 36% in the general population. Use of OTC medicine with acetaminophen did not differ across the cohorts (30–34%). All three cohorts were unlikely to correctly identify drugs containing acetaminophen but the opioid cohorts performed better than the general population. Those with higher education performed slightly better when asked to identify acetaminophen products than those with no college education. The average usual daily dose (mg/day) reported was highest in the long-term opioid cohort (1,185), followed by the acute opioid cohort (1,010) and the general population (891) – $p < 0.001$. Estimated supratherapeutic exposure was rare but 3–5 times more common in the opioid cohorts than in the general population.

Conclusions: Acetaminophen use is common and supratherapeutic exposure may be of concern in opioid users. Knowledge of which drugs contain acetaminophen appears inadequate; better labeling and proactive education from professionals may be impactful.

903. Non-Steroidal Anti-Inflammatory Drug and Aspirin Use and the Risk of Head and Neck Cancer

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Background: The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with a reduced risk of several cancers. Evidence for NSAIDs preventing head and neck cancer (HNC) is inconclusive.

Objectives: To examine the effect of aspirin and other NSAIDs on the risk of HNC, by means of a large scale prospective investigation using data from the National Cancer Institute (NCI) Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Methods: Using data from the NCI PLCO Cancer Screening Trial, we examined the association between aspirin/NSAID use and HNC incidence among 142,034 men and women aged 55–74 years. Information regarding regular use and frequency of use of aspirin and NSAIDs over the last 12 months was reported at enrolment (1993–2001). Individuals were followed up until 2006. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using multivariable cox proportional hazards regression with adjustment for potential confounders including tobacco use, gender, body mass index and age.

Results: Over the follow up period 316 individuals were diagnosed with HNC. Regular aspirin use, compared to non-use, was associated with a significantly reduced incidence of HNC (Adjusted HR = 0.78; 95% CI = 0.62–0.98). No association was observed with regular NSAID use, compared to non-use, and HNC incidence (adjusted HR = 0.99, 95% CI 0.76–1.28).

Conclusions: Our study suggests that aspirin may have potential as a chemopreventive agent for HNC however further investigation is warranted.

904. Non-Steroidal Anti-Inflammatory Drug and Aspirin Use and the Risk of Malignant Melanoma – A Systematic Review and Meta-Analysis

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Background: Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with a reduced risk of several cancers. Evidence from experimental studies suggests NSAIDs may prevent malignant melanoma (MM) development.

Objectives: To conduct a systematic review and meta-analysis to assess whether the use of aspirin and/or other NSAIDs is associated with the risk of developing MM.

Methods: Medline, Embase, PubMed, Cochrane Library and Web of Science were systematically searched using terms for NSAIDs/aspirin, MM and observational/intervention study designs to identify studies published to September 2010. When possible, adjusted results were combined by using random-effects meta-analyses.

Results: Of 8992 articles identified, nine studies met the selection criteria. These included 5 cohort studies, three case–control studies, and one randomised controlled trial (RCT). The results of the overall pooled analyses found no evidence of an association between MM risk and the use of either NSAIDs (including aspirin) (relative risk (RR) 0.99, 95% CI 0.91–1.08), aspirin (RR 1.00, 95% CI 0.89–1.12) or non-aspirin NSAIDs (RR 1.07, 95% CI 0.97–1.17). Sub-analyses by duration of use or dosage could not be conducted due to inconsistencies in the definitions of dosage and duration.

Conclusions: In conclusion, the results of this systematic review and meta-analyses do not strongly suggest an association between the use of NSAIDs, either aspirin or non-aspirin NSAIDs, and the risk of MM.

905. Pain Management: Observation and Side Effects

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Background: Pain treatment is a real challenge for Public Health and a requirement for the quality and evolution of a health system. Itresponds primarily to a humanist and ethical objective, intrinsic to the dignity of the humankind. The physical pain and moralsuffering experienced during all ages of life make those already weakened by the disease even more vulnerable. Treatmentcompliance is essential to the efficacy of the treatment offered. Side effects or undesirable effects may be caused by noncompliance when they appear in the first 24 or 48 hours after treatment.

Objectives: The objective is to describe the side effectsperceived during the first 48 hours and spontaneously cited by the subjects treated with an analgesic.

Methods: Prospective, longitudinal, multicenter observational study, conducted in France using data collected by the generalpractitioners who agreed to participate.

Results: Patients were treated either with a paracetamol-codeine combination (n = 742) or with a paracetamol-tramadol combination (n = 107). Nausea/vomiting, dizziness, drowsiness and constipation were the 4 most commonly cited side effects. In the firstgroup, prevalence after 24h was 9.56%, 2.96%, 4.44% and 1.08% respectively, vs. 13.89%, 7.41%, 2.78% and 2.78%in the second group. On the 2nd day, prevalence in the first group was 3.9%, 2.01%, 3.4% and 2.8% respectively, vs.11.1%, 3.7%, 1.85% and 2.78% in the second group. Prevalence of at least one side effect perceived during the 7 days oftreatment was 29.74% in the first group vs. 40.74% in the second treatment group.

Conclusions: A study published in 2005 (Patients and chronic pain – Exercer magazine January 2005 – Le Goaziou et call) indicated 37%constipation, 24% nausea and vomiting and 22.4% dizziness for a group of patients undergoing treatment. It appeared thatthe patients treated with one of the two drug combinations had fewer complaints of the same side effects.

906. Trends in the Frequency of Gastrointestinal Perforation in a Cohort of Patients with Rheumatoid Arthritis

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Background: Gastrointestinal perforation (GIP) is a rare but serious safety-related event in patients treated with an array of rheumatoid arthritis (RA) medications.

Objectives: To trend the age-adjusted rate of GIP over time using a large US claims database.

Methods: Patients aged ≥18 years were selected from MarketScan® claims databases (2002–2008) with ≥2 RA (ICD-9-CM 714.0, 714.3) diagnoses within 30 to 365 days and ≥1 year of continuous enrollment. Patients who were hospitalized for GIP or who had any evidence of gastrointestinal malignancy at baseline were excluded. Patients were followed up until the date of GIP, database disenrollment, or study end. A validated algorithm identified the first hospitalized GIP event (upper or lower GI). Age-adjusted GIP rates were calculated for each calendar year and by exposure to glucocorticoids. Rates were reported per 1,000 person years (PY) of observa-

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tion. The Cochran-Armitage test was used to assess time trend.

Results: The study population included 143,433 RA patients: mean age, 57.7 (SD 14.1) years; 74.8% female; median follow-up, 2.5 years. Hospitalization with GIP occurred in 0.5% of patients (n = 696), with 6.6% of patients dying during the admission. The GIP rate per 1,000 PY was 1.7 (95% CI, 1.6–1.9). The majority of events were in the lower GI tract (1.44; 95% CI, 1.32–1.55). The age-adjusted average annual GIP rate numerically decreased from 2.1 per 1,000 PY (95% CI, 1.4–3.1) in 2002 to 1.8 (95% CI, 1.5–2.1) in 2008. GIP rates were significantly higher during periods of current exposure to glucocorticoids during the follow-up period, 2.4 per 1,000 PY (95% CI, 2.2–2.7) vs. 1.4 per 1,000 PY (95% CI, 1.2–1.5). The age-adjusted average annual GIP rate during periods of glucocorticoid exposure decreased from 3.5 per 1,000 PY in 2002 to 2.8 per 1,000 PY in 2008 while increasing from 1.2 to 1.3 per 1,000 PY during the same time frame in periods of no exposure. No time trends were significant.

Conclusions: Despite the introduction of a number of new therapies during the past decade, the age-adjusted rate of GIP has not increased significantly, even after stratification by glucocorticoid use.

907. Cohort Entry Criteria and Co-Morbidities in a Claims-Based Male Osteoporotic Population

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Background: Osteoporosis (OP) in men remains poorly understood despite considerable morbidity and mortality associated with the disease. There is a paucity of data related to both the identification of male OP in claims databases, particularly in younger men, and the background incidence of co-morbidities often considered potential adverse events (AEs) in OP drug safety studies.

Objectives: To describe cohort entry criteria for OP men and to compare the incidence of nine selected AEs in the overall and osteoporotic male populations.

Methods: We identified a 7% random sample of men ≥30 years old, excluding cancer cases, from a large health insurance population enrolled between October 1, 2005 and December 31, 2010. Within this overall cohort, we identified men with a diagnosis code for OP, treatment with an OP medication, or an OP-related fracture. We estimated the frequency of each OP cohort entry criterion by age, and calculated age-standardized and age-stratified incidence rates (IRs) of selected AEs in each cohort.

Results: Of the 502,370 eligible men, 64,708 met the OP criteria**.** OP fracture was the most frequent cohort entry criterion (49%), with the 30–49 year age group having the highest percentage of men identified via OP fracture (68%). A diagnosis code for OP was the least frequent means of OP identification across most age groups. The IRs of most AEs were higher in the OP cohorts than the overall cohort, including subtrochanteric/diaphyseal femur fractures (494.3 vs. 24.1/100,000 PY), fracture healing complications (771.4 vs. 41.5/100,000 PY) and acute pancreatitis (178.4 vs. 80.6/100,000 PY). Many IRs varied by age.

Conclusions: It is important to include fracture and treatment in addition to diagnosis as entry criteria for male OP cohorts. However, further study is necessary to understand whether the large percentage of men identified by fracture in the 30–49 year age group is a result of the inclusion of traumatic fractures or as a result of underdiagnosis of OP. The varying IRs of potential AEs by cohort and age highlight the need for appropriate comparison groups when conducting observational studies.

908. Digital Ulcers Outcome Registry (DUO) in Patients with Systemic Sclerosis (SSc): Methodology To Characterize Patients in Terms of Recurrence of Digital Ulcers (DU)

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Background: Patient-reported surveys suggest around half of systemic sclerosis (SSc) patients are affected by digital ulcers (DUs) during their lifetime. Recent reports confirm around 30% of those with SSc suffer from at least one DU episode each year. The DUO Registry is a European, multicentre, prospective, observational, cohort study of SSc patients with ongoing DU disease.

Objectives: To explore definitions of DU disease recurrence phenotypes based on the frequency of DUs in SSc patients. To determine a methodology to define the burden of clinical disease across SSc-DU recurrence phenotypes.

Methods: The registry enrols patients with current or a history of DU. Patients are clinically assessed, receive medical care and visit schedules as determined by their physician. Since April 2008, data collected at enrolment and during follow-up include: demographics; SSc characteristics; history of DU disease; DU-related interventions/complications (which characterise disease severity); ongoing medications and number of DU at the time of enrolment. The total number of DU on fingers and the month of any new DU occurring between visits were recorded specifically at follow-up visits.

Results: Patients were defined by the DU recurrence phenotypes observed during a 2-year time window from enrolment (start of follow-up): (1) no DUs in follow-up; i.e., no DUs at follow-up visits and no new DUs occur between visits; (2) episodic: only one follow-up visit with a DU; (3) recurrent: frequent and regular DU with at least two visits with DU and at least one visit with no DU; and (4) chronic: DU are present at every follow-up visit. DU recurrence phenotype will be further characterised by disease severity characteristics in order to determine plausibility, relevance and validity of SSc-DU recurrence definitions.

Conclusions: In this rare disease prospective registry setting, proposed definitions of disease recurrence based on event frequency over time are explored. Such patient disease characterisation is needed for both clinical trial planning and real-world management of SSc-DU patients.

909. Risk Factors Associated with Allopurinol Related Stevens-Johnson Syndrome – A Case Control Study in Taiwan

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Background: Allopurinol related severe cutaneous adverse reaction of Stevens-Johnson Syndrome (SJS) is the most common cause for cases submitted to the Drug Relief Foundation for compensation in Taiwan Risk factors of allopurinol users to develop the potentially life-threatening Stevens-Johnson Syndrome among the Taiwanese population have not been well studied.

Objectives: To investigate patient characteristics and comedications associated with allopurinol induced Stevens-Johnson Syndrome.

Methods: A nested case–control study was carried out with the database of National Health Insurance in Taiwan Study population included new users of allopurinol between 2001 and 2004. Patients with diagnosis of Stevens-Johnson Syndrome (ICD-9 code 695.1x) while on allopurinol treatment and discontinued the allopurinol thereafter were defined as cases. Each case was matched up to 20 controls by age, sex, and time of initiation of allopurinol treatment. Conditional logistical regression was used to identify factors associated with an increased risk of Stevens-Johnson Syndrome.

Results: In total, 335 cases with 6,409 match controls were identified from 579,281 new users of allopurinol during the study period. The incidence rate of allopurinol related SJS was 3.7 per million person-year. Factors related to the renal function were found to be significantly associated with allopurinol induced SJS in unadjusted analyses. The adjusted results showed that factors increased SJS risks were renal disease (OR 2.42, 95% CI: 1.88–3.14), diuretics use (2.35, 1.82–3.05), aminoglycoside use (1.97, 1.24–3.13), and amoxicillin use (1.98, 1.48–2.65). There was no significant dose-response effect between allopurinol and Stevens-Johnson Syndrome (OR = 1.0).

Conclusions: Patients using medications and/or with underlying diseases that could compromise renal function are at higher risk for allopurinol induced Stevens-Johnson Syndrome.

910. Impact of Gastroesophageal Reflux Disease (GERD) Definition on Incidence Rate of Endoscopies among Osteoporotic Patients

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Background: Gastroesophageal reflux disease (GERD) is a known confounding factor when investigating cancer of the esophagus since both involve use of endoscopies during diagnosis. Identification of GERD cases when using observational databases has been done using various algorithms, which involve the use of diagnosis codes and proton pump inhibitor prescriptions that are used in the treatment of GERD.

Objectives: To assess the impact of GERD definition criteria on the incidence rate of endoscopies among patients with a diagnosis of osteoporosis.

Methods: The study looks at a cohort of 7,781 female patients aged 50 years and above with osteoporosis who received an endoscopy in the General Practice Research database (GPRD). Of 2,460 of the patients had at least 1 of the following GERD definitions: At least one GERD diagnosis code; two diagnoses codes; one diagnosis code and a PPI prescription; 2 diagnosis codes and a PPI prescription; a diagnosis code and five PPI prescriptions and a diagnosis code and 10 prescriptions of PPI. Endoscopy incidence rates among the above were calculated.

Results: Among osteoporotic patients, having at least 1 diagnosis of GERD increases the incidence rate of endoscopies threefold from 0.83 (0.80–0.84) to 2.56 (2.46–2.66) per 100 person years. Doubling the number of diagnoses in the criteria increased the incidence rate from 2.56 (2.46–2.66) to 3.32 (3.13–3.51) per 100 person years. However inclusion of a PPI prescription to one diagnosis code 3.07 (2.88–3.26) or two diagnoses codes 3.68 (3.39–3.99) didn't increase the endoscopy incident rate significantly.

Conclusions: Definition of GERD should be taken into account when studying cancer of the esophagus. The number of PPI prescriptions doesn't affect the incident rates

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possibly because of the abundance of over the counter PPI availability in the UK.

Validation of various GERD definitions should be considered when using a database that can access source records.

911. Prescribing and Administration of Parkinson's Disease Medications

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Background: One in three people with Parkinson's disease (PD) are admitted to hospital annually; many are subject to inadequate medicines management. The UK Parkinson's Disease Society "Get it on time" campaign and a 2010 UK National Patient Safety Alliance report emphasise the importance of administering PD medicines on time to reduce harm.

Objectives: To assess the prescribing and administration of PD medication in various NHS Greater Glasgow and Clyde (GGC) hospital sites

Methods: A multi-disciplinary group set the standards and criteria for this audit based on those from Parkinson's UK. Data were collected prospectively for 28 patients, through convenience sampling, by pharmacists for 1 week of the patient's in-patient stay during February to March 2011. Patients were identified from within Emergency Care and Medical Specialities and Surgical and Anaesthetic wards at one NHSGGC site and from Rehabilitation and Assessment wards across NHSGGC. Cases, where PD drugs were given late, were referred to a PD specialist for interpretation. Data were analysed by comparing results to the agreed standards and criteria.

Results: A medicines reconciliation policy was reported to be in place in all sites where data were collected. Drug history was checked within 24 hours of admission in 60% of cases. The first dose of PD medication after admission was administered on time in 62% of cases falling short of the recommended standard of 90%. On average two doses of PD medications were omitted per patient during 1 week of data collection, although the 90% standard was met (93%) there is potential for improvement. The prescribing of contraindicated medicines occurred once. None of the wards were implementing self administration.

Conclusions: The findings highlight areas for improvement. An action plan has been developed to address these. This includes the development of PD guidance for inclusion in the local NHSGGC Therapeutics Handbook, updating the emergency PD stock lists, delivering education to medical, pharmacy and nursing staff to raise awareness of the audit results, communicating the key messages of this audit via NHSGGC educational bulletins and finally performing a re-audit to measure improvement in practice.

912. Benzodiazepine Use and Risk of Dementia: A Prospective Population-Based Cohort Study

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Background: The existence of long-term adverse effects of benzodiazepines (primarily indicated against symptoms of anxiety and sleep disorders) on cognition, including dementia is debated.

Objectives: To evaluate the association between new initiation of benzodiazepines and incident dementia.

Methods: A 15-year follow-up was set up within the PAQUID population-based cohort study (South-Western France). Out of the 3,777 participants aged 65 and over, we selected those (n = 1063, mean age = 78.2 years) who were free of dementia and did not initiate a benzodiazepine (BZD) up until the 5th year (T5) of follow-up (baseline for this study). The new BZD initiators (n = 95) at T5 were compared to non-initiators (n = 968) on a 15-year follow-up basis, the main outcome being incident dementia assessed at each follow-up. Multivariate Cox proportional hazard models were used to estimate the association with control of the main potential confounders measured at baseline (age, sex, schooling duration, marital status, wine consumption, depressive symptomatology, cognitive evolution trend, high blood pressure, diabetes mellitus, statin use, antithrombotic use).

Results: During a mean of 6.2 years of follow-up, 253 incident dementia cases were confirmed. New initiation of benzodiazepines was associated with an increased risk of dementia (multivariable-adjusted hazard ratio [HR] = 1.63; 95% CI = 1.11–2.41). Sensitivity analyses considering the existence of depressive symptoms led to similar results (HR = 1.64; 95% CI = 1.10–2.45). In a secondary analysis considering different cohorts of benzodiazepine users according to time of initiation (at baseline and during subsequent follow-up), the pooled HR for incident dementia was 1.46 (95% CI = 1.10–1.93).

Conclusions: In this prospective population-based cohort study, new initiation of benzodiazepines was associated with increased risk of dementia. Considering the high utilization of benzodiazepines and increasing incidence of dementia in the general population, indiscriminate widespread use of benzodiazepines should be cautioned against.

913. Length of Hospital Stay of Patients with Schizophrenia: Relation to Antipsychotic Monotherapy vs. Polypharmacy

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Background: We have previously observed that inpatient drug treatment for schizophrenia differed across three European countries (Spain, Estonia and Sweden). We also observed that high antipsychotic dosages as well as antipsychotic polypharmacy should be avoided (except for short periods when switching antipsychotics) because these practices are associated with an increase in the risk of adverse effects, drug-drug interactions and mortality (Llerena et al., 1993).

Objectives: To evaluate the differences between patterns of antipsychotic drugs use (monotherapy vs. polypharmacy and typical vs. atypical antipsychotic medication) in relation to the timing of hospital stay in inpatients with schizophrenia.

Methods: The medical records of all consecutively admitted patients to ''Infanta Cristina'' Hospital (Badajoz) and ''Díaz Ambrona'' Hospital (Mérida) receiving a diagnosis of schizophrenia (DSM-IV criteria upon discharge) during a ten-year period (2001–2010) were studied. The prescribed treatment regimens (polypharmacy, and typical/atypical antipsychotics) were retrospectively analysed. From with the diagnosis of schizophrenia were reviewed.

Results: A total of 1044 patients that were hospitalized received a diagnosis of schizophrenia during 2001–2010. Of them, 526 (50.4%) received monotherapy. In particular, most patients were treated with atypical antipsychotic monotherapy (425, 40.7%). Mean length of stay was on average more than a week longer for those taking antipsychotic polytherapy (29.6 ± 38.3) than for those under antipsychotic monotherapy (21.5 ± 27.6).

Conclusions: Inpatients with schizophrenia under antipsychotic polypharmacy had on avarage more than 4 weeks of hospital stay whereas those under antipsychotic monotherapy stayed about 3 weeks.

914. Timing of Concomitant Drug Use in Pharmacoepidemiological Studies

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Background: Both antidepressants (AD) and benzodiazepines (BZD) have been associated with an increased risk for hip fracture. However, the hazard function is not constant over exposure time and differs for these two medication classes. Hence, the timing of initiation of co-use will determine the overall hazard function.

Objectives: The aim of this study was to describe timing of BZD co-medication use among AD users.

Methods: The study population included patients from the Netherlands Information Network of General Practice who initiated ADs between 2002 and 2009. AD-treatment episodes were constructed for each patient assuming the start of a new episode when 90 days elapsed between the theoretical end-date of a prior AD prescription (Rx) and the start-date of the next AD Rx. Within the first AD episode, three groups of BZD co-use were defined: ''simultaneous'' (simultaneous start of AD and BZD, no BZD during 182 days prior to start), ''before'' and ''during'' starters. These groups were described according to intensity of BZD use (number of Rxs), mono/polytherapy of AD and duration of AD episode.

Results: The study population consisted of 16,617 AD users. The mean age was 50 years (SD = 18) and 63.2% were female. The median duration of the AD episode was 80 days (IQR = 259). Of 28.5% of patients used both AD and BZD. Of these, 57.2% started BZD before the AD, 19.0% were ''simultaneous'' starters and 23.8% started BZD during their first AD episode. In general, ''simultaneous'' starters were younger (mean = 45.3 vs. 56.4 years) yet had less intensity of BZD use (mean = 4.3 vs. 7.5 Rxs) compared to ''before'' starters. ''After'' starters were slightly older (mean = 48.0 vs. 45.3 years), had more AD polytherapy (20.2% vs. 14.9%) however less intensive BZD use (mean = 3.7 vs. 4.3 Rxs) compared to ''simultaneous'' starters.

Conclusions: Timing of initiating BZD use in AD users is important, as each BZD co-use group is expected to have a different overall hazard function for hip fracture as opposed to when co-medication is defined as constant over time. To calculate accurate hazard function, it is important to take into consideration the timing of initiation of co-medication use in pharmacoepidemiological studies.

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915. Pharmacological Treatment and Demographic Characteristics of Adult Patients with Attention Deficit Hyperactivity Disorder, Sweden

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Background: An increasing number of adults are diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). None of the available drugs are approved for treatment of adults with ADHD in Sweden and knowledge concerning those who treated for ADHD is limited.

Objectives: To describe the adult populaton with ADHD and their pharmacological treatment.

Methods: Using the Swedish Patient Register and the Prescribed Drug Register we identified individuals 19 years of age or older who were diagnosed or medically treated for ADHD for the first time 2006–2007. The subjects were followed from entry to December 2009. The unique patient identifiers were used to link information from the two registers to describe demographic characteristics, hospital care and drug treatments. Logistic regression model estimated the association between age, sex, frequency of hospitalization, diagnosis or treatment for other psychological disorders and risk of gap and discontinuation of the treatment.

Results: Totally the study included 6,069 patients of whom 60% were males, mean age at entry to the study was 34 years (SD = 12) and median was 32 years (IQR 24–42). Some 81% were medically treated for ADHD, approximately 85% received methylphenidate as the first substance and combination therapy was rare (1.98%). More than 59% of the patients, which could be followed up for 2 years after start of treatment (n = 4,324), had at least one treatment gap of 6 months. Some 49% of medically treated patients discontinued the medication. More than 73% had comorbidity or treatment for other psychological disorders. The comorbidity decreased risk of being medically treated (0.7, 95% CI 0.6–0.9). Male sex, age under 25 years at entry and lower number of hospitalizations increased risks of gap and discontinuation of medication. Medical treatment for other psychological disorders extensively increased risk of discontinuation (20, 95% CI 14–29).

Conclusions: Approximately one fifth of the adult patients recorded in the Swedish Patient Register as diagnosed with ADHD did not receive medical treatment for their disease. Medication adherence seems to be low particularly in younger patients.

916. Treatment of ADHD with Psychostimulants in Patients on Opioid Maintenance Therapy (OMT) in Norway – A Nationwide Study

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Background: The Norwegian opioid maintenance therapy (OMT) model was implemented in 1998. Attention Deficit Hyperactivity Disorder (ADHD) is a major risk factor for the development of substance use disorders. Treatment of ADHD with psychostimulants in OMT patients is challenging and has been restricted in Norway.

Objectives: To study the use of ADHD drugs in OMT patients in Norway and to explore comedication with antidepressants, hypnotics and anxiolytics in this population.

Methods: Data were drawn from the nationwide prescription database (NorPD) which includes all filled prescriptions in Norwegian pharmacies. The study population consists of people >18 years who were dispensed either methadone mixture (ATC code N07BC02), buprenorphine capsules (N07BC01) or buprenorphine-naloxone combined capsules (N07BC51) during 2004–2010. The following psychostimulants and other psychotropic drugs were included: racemic amphetamine (N06BA01), dexamphetamine (N06BA02), methylphenidate (N06BA04), atomoxetine (N06BA09), antidepressants (N06A), anxiolytics (N05B) and hypnotics (N05C). Variables included: patient's unique identity number (encrypted), gender, age, ATC code, and date of dispensing. One-year prevalence of treatment was calculated. The observed number of patients treated with psychostimulants was compared to the expected number calculated by applying the prevalence for each sex and age specific group in the general population on the sex and age distribution in the study population.

Results: Number of patients in OMT increased in the period and reached 6,116 in 2010. Of these, 170 patients (2.8%) were treated with psychostimulants, seven times higher than expected in the general population. Methylphenidate was by far the most commonly used ADHD drug in OMT patients, followed by atomoxetine. Sixty percent of the OMT patients filled at least one prescription for antidepressants, anxiolytics or hypnotics in 2010 and the percentages were similar for users and non-users of ADHD drugs.

Conclusions: The treatment with psychostimulants was more common OMT patients than expected in the general population of Norway. Comedication with other psychotropics was also common in OMT patients.

917. Inpatient Treatment of Schizophrenia during 2001–2010: Average Length of Stay, Use of Diagnostic Tests and Drug Treatment

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Background: Schizophrenia generates a great global burden for the social care system. In terms of health care financial expenses, schizophrenia is the most costly psychiatric disease. In particular, the inpatient care costs of schizophrenia can be estimated by firstly analysing the length of hospital stays, use of diagnostic tests and drug treatment. In keeping with this fact, we have previously observed that inpatient drug treatment for schizophrenia differed across three European countries (Spain, Estonia and Sweden).

Objectives: To determine the evolution of the mean length and number of hospitalizations, and of the use and type of diagnostic tests and antipsychotic drug treatment for patients with schizophrenia in a region of Badajoz (Spain).

Methods: The medical records of all consecutive patients receiving a diagnosis of schizophrenia (DSM-IV criteria upon discharge), who were hospitalized in ''Infanta Cristina'' (Badajoz) and ''Díaz Ambrona'' Hospitals (Mérida) during a 10-year period (2001–2010) were studied.

Results: A total of 1,791 medical records of hospitalized schizophrenia patients were reviewed. The mean lenght of hospitalization ranged from 37.6 days in 2004 to 18.3 days in 2006, with an avarage stay of 4 weeks (27.9 days) relatively stable during the whole 10-year period. The average number of the most frequently used diagnostic tests per 100 admissions was 67.7 biochemical markers, 65.5 hematologic indices, 46.2 urine, 42.3 coagulation (42.3), and 40.6 cardiac electrogram. The most prescribed antipsychotic drugs during this period per percent of total days in hospital) were: olanzapine (42.4), risperidone (28.6), quetiapine (16.6) and levomepromazine (16.4).

Conclusions: The average length of hospital stay was about 4 weeks during the 10 years period. The biochemistry and hematologic tests and the second generation antipsychotics olanzapine and risperidone were the most frequently prescribed. The relevance of present data on the cost of the inpatient treatment of schizophrenia and the clinical outcome will be considered in a prospective study.

918. Effects of Recent Earthquake on the Prescribing Pattern of Antidepressant and Antipsychotic Drugs in the Southern Italian Province of L'Aquila

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Background: Natural disasters provoke an increase in mental and medical disorders in survivors. Careful monitoring of drug use may be required in these situations.

Objectives: To assess the effects of earthquake that occurred on April 6, 2009 on the use of antidepressant and antipsychotic drugs in the province of L'Aquila.

Methods: We conducted a cross-sectional, drug utilization study. Data sources of this study were the dispensings database of the Southern Italian Local Health Unit (LHU) of L'Aquila and Caserta. All the antidepressant and antipsychotic drugs (except for prescriptions in dementia patients) are reimbursed by Italian National Health System and therefore are retrieved in such a database. We measured the monthly prevalence of use of these drugs 1 year prior and after the date of earthquake in L'Aquila LHU. We used as control the LHU of Caserta, as this area was not affected by the earthquake. All the analyses were stratified by age groups, gender and drug classes (Selective Serotonin Reuptake Inhibitors, Tryciclics, and other ADs; atypical and typical antipsychotics).

Results: Overall, the monthly prevalence of use of ADs and APs was higher in L'Aquila than Caserta. With respect to trend over time, we observed an increase in the use of antidepressants (mostly tryciclics) and antipsychotics (mostly typicals) in the first 2 months after the earthquake in L'Aquila but not in Caserta. This increase was almost twofold higher in women older than 75 years. The use of ADs and APs in general tended to decrease in the summer period in Caserta, while such a trend was not observed in L'Aquila after the earthquake. After the first 2 months from the earthquake, the use of ADs and APs is stabilized at the pre-earthquake levels in L'Aquila.

Conclusions: The earthquake determined a very short term increase in the use of antidepressants and antipsychotics mostly in older women of L'Aquila.

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919. Prevalence and Patterns of Antidepressant Use among Women of Reproductive Age in Northern Ireland (NI)

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Background: Antidepressant use prevalence represents both the prevalence and treatment of depression. Monitoring patterns of antidepressant use can help inform policies regarding prevention of depression and its appropriate treatment.

Objectives: To determine the 1-year prevalence of antidepressant drug prescription among women of childbearing age (15–45 years) in Northern Ireland (NI), and the proportion with co-administration of psycholeptic drugs, and to identify socio-demographic factors associated with antidepressant prescription.

Methods: A cross-sectional study design was applied to Electronic Prescribing and Eligibility System prescribing data in 246 out of 363 GP practices with high coverage (≥70%) of electronic prescribing data in NI. Socioeconomic deprivation data were obtained from the 2010 NI Multiple Deprivation Measure for area of residence. The study population consisted of women of childbearing age in these practices registered with the same GP practice throughout the study period with or without antidepressant medication. Outcome measures were the levels of antidepressant prescribing and co-prescribing of psycholeptics in a 1-year period and socio-demographic factors associated with them. Logistic regression modelling was employed in establishing the variation of antidepressant use with socio-demographic factors.

Results: A 1-year antidepressant prescription prevalence of 16.3% (95% CI 16.1–16.4) in 268,917 women of childbearing age in 2009 was estimated. Antidepressant prescription prevalence increased from 4.8% in the 15–19 years age group to 24.6% in the 40–45 years age group and from 13.5% in women living in the least socioeconomically deprived areas to 20.7% in those in the most deprived areas. Women who accessed GP practices in urban areas were more likely to receive a prescription for an antidepressant. Of 34.8% of the women who received prescriptions for antidepressants were co-prescribed with a psycholeptic medication.

Conclusions: NI is an area of high antidepressant use. These data reinforce the need to address the determinants of depression, and treatment policies and practices.

920. Trends in Use of Benzodiazepines, Opioids, Tramadol, and Z-Drugs from 1998 to 2008 in a Managed Care Population

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Background: Benzodiazepines, opioids, tramadol, and z-drugs (BOTZ drugs) have known, serious side effects as well as potential for dependency. BOTZ polypharmacy is thought to be increasing in younger populations and may result in severe consequences.

Objectives: To describe the BOTZ utilization patterns among young adult women including exposure to any two different classes of BOTZ drugs in a given year over time.

Methods: We conducted a study among young women in the IMS Lifelink™ Health Plan Claims Database from 1998 to 2008. Patients were included if they were above the age of 18. Based on pharmacy claims data, we report overall and annual prevalence for each drug class, and for exposure to of any two different BOTZ drug classes. The trend in exposure was evaluated using linear regression.

Results: The average enrollment time in one of the plans captured by the IMS database was 1.95 years (IQR 0.58–2.83) and the average age at enrollment was 29.9 (IQR 25–35). Out of 5,821,583 women, 1,515,895 (26.0%) were identified to have at least one prescription for any of the medications of interest. The overall use (at least one Rx) of opioids, benzodiazepines, tramadol, and z-drugs was 22.7%, 7.2%, 2.7%, and 1.9%, respectively. Over a decade, the percentage of women exposed to each class increased annually, ranging from 8.5% to 15.4%, 1.6% to 5.9%, 0.4% to 2.0%, and 0.2% to 0.7%, respectively. Exposure to two different BOTZ drug classes increased fivefold, from 0.8% to 4.3% ($p < 0.01$ for trend) between 1998 and 2008.

Conclusions: Despite cautions regarding risks of BOTZ drug polypharmacy, our study identifies increased rates of exposure to more than one BOTZ drug. Increased vigilance is warranted for screening patients taking multiple BOTZ drugs to ensure benefits outweigh risks.

921. Analyses of Switching and Combination Use of Antidepressants in Young Swedish Adults

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Background: Previous studies report varying frequency of switching and combination use of antidepressants between age groups and by socioeconomic characteristics.

Objectives: To analyse frequency of and predictors for combination use and switching of antidepressants in Swedish adults aged 20–34 years.

Methods: The study population encompassed antidepressant users aged 20–34 years initiating use between January and June 2006 (n = 24,897). Data on filled antidepressants in 2006 were collected from the Swedish Prescribed Drug Register and information on socioeconomic characteristics from Statistics Sweden. Clinical and socioeconomic factors associated with use of at least two antidepressants and switching were analyzed with multivariate logistic regression.

Results: In total, 17.1% purchased at least two antidepressant drugs. This was more common among women, odds ratio (95% confidence interval): 1.16 (1.04–1.28), among those who started on mirtazapine compared to SSRIs: 2.33 (2.01–2.71), when a psychiatric care facility issued the index prescription compared to primary care 1.19 (1.07–1.32), among those born in Sweden with one parent born in Sweden 1.26 (1.09–1.45) and those who had received social assistance 1.19 (1.03–1.37). It was less common when an occupational health facility issued the index prescription 0.70 (0.53–0.94), with declining length of follow up 0.73 (0.62–0.86), and with increasing length of education. Among those who used at least two antidepressants, 71.6% were classified as switchers. Switching was less common among those starting on mirtazapine: 0.69 (0.53–0.90), when the first prescription was issued in psychiatric care 0.74 (0.60–0.90) and among individuals with at least 2 years of university education 0.60 (0.41–0.87).

Conclusions: Almost one fifth used two or more antidepressants; the majority was classified as switchers. Type of starting antidepressant, whether the index prescription was issued by a psychiatric care facility and level of education influenced use of at least two antidepressants and switching.

922. Utilization Patterns of Strattera in Germany, Netherlands, Sweden and UK

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Background: There is limited information on Strattera utilization in European countries.

Objectives: To assess Strattera utilization patterns among new users of the drug in Germany, Netherlands, Sweden and UK from 2006 to 2011.

Methods: Data sources for this retrospective study included: LRx longitudinal prescription data in Germany and Netherlands, General Practice Research Database (GPRD) in UK, and CEBRxA database in Sweden. A cohort of new users of Strattera in these databases was created and followed for a 2 years period after drug initiation over the last 2 years of available data. We estimated: number of initiators, comorbidities, mean length of therapy (LOT), persistence (actual days supply prescribed/dispensed), and adherence (Proportion of Days Covered [PDC]).

Results: During the study period the number of new Strattera users increased in Netherlands and Sweden, was relatively constant in UK, and decreased in Germany. The mean (range) of Strattera initiators was: Germany 16,958 (12,053–24,080), Netherlands 6,918 (3,963–8,465), UK 761 (689–805), Sweden 305 (242–368). In all countries, the drug was more commonly prescribed to persons aged 6–17 years (73–83%) than adults ≥18 years (8–26%). The most common comorbid psychiatric condition in UK was mental disturbance NOS (30.0%) and in Sweden was depression (27%). No cardiovascular comorbidities were reported in UK, and were uncommon in Sweden. The overall mean LOT (days) during the 2-year follow-up period was: UK (396.4), Sweden (300.8), Germany (282.8) and Netherlands (241.3). Persistence 1-year after drug initiation was: Germany (49.2%), UK (47.0%), Netherlands (26.9%), and Sweden (26.6%). Adherence (compliance) based on PDC during the 2 year study period was: UK (57.0%), Germany (39.0%), Sweden (38.0%), and Netherlands (33.0%).

Conclusions: Strattera usage in the studied countries appears to be confined to relatively short periods of time and with a low rate of treatment reinitiation.

923. Assessing the Effect of a Guideline Change on Prevalence of Benzodiazepine Use by Including the Birth Cohort Dimension

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Background: The effect of guideline changes on trends of prescription drug use are commonly studied by age and over time period. This masks the birth cohort dimension which affects the age-specific trends in each time period.

Objectives: We investigated whether including the birth cohort dimension in time series analysis leads to a more accurate estimation of the effect of a guideline change on the trend of benzodiazepine use.

Methods: Outpatient pharmacy data from a drug prescription database in the Netherlands (IADB.nl) were used to obtain the age- (18–85) and sex -specific number of users of benzodiazepine (ATC: N05BA and N05CD) per 1,000 population (prevalence) per quarter year from 1998 to 2008. We studied the prevalence over time by age

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groups and by birth cohorts. Interrupted time series analyses were performed to the de-seasonalized trend to estimate the effect of the guideline change in 2001.

Results: From 1998 to 2008 the overall age-standardized prevalence of benzodiazepine use per 1,000 population declined from ˜55 for males and ˜105 for females to ˜42 for males and ˜78 for females, this decline strengthened in 2001 for both sexes (significant slope change of $p < 0.05$). Similar patterns over time, including slope changes ($p < 0.05$), can be found within the majority of age categories, providing no additional information. Within birth cohorts the prevalence first increased over time but after 2001 this increase stopped or weakened ($p < 0.05$), indicating a reduction in starters or less chronic use of benzodiazepine.

Conclusions: Studying trends within birth cohorts can be a useful addition to time series analyses because the same or similar individuals are followed over time, making analysis more intuitive. This is not the case for trends within age-categories, potentially leading to less informed conclusions about guideline effects.

924. Hypnotic Drugs Use and Quality of Life: Longitudinal Analysis from the VISAT Cohort

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Background: Throughout the world, hypnotic drugs do not have the indication for chronic insomnia. This is based on the tolerance to their hypnotic effects and on the risk of pharmacodependence. In addition to pharmacodependence, the reason of high prevalence chronic use of hypnotic drugs could be related to a positive effect on the quality of life (QoL) of users.

Objectives: To evaluate the association between chronic use of hypnotic drugs and the evolution of QoL, in a population of workers of three areas of Southern France.

Methods: This study included 1257 French workers from the VISAT[1] (Ageing, Health and Work) cohort. The evolution of QoL scores (using the Nottingham Health Profile) after a 5 years follow-up (2001–2006) was investigated among two categories of hypnotic drugs users: "non-consumers" (no consumption at the two data collection times) and "chronic consumers" (consumption of at least 1 year declared in 2006) with logistic polytomic regression models adjusted for several potential confounders. The drugs studied were all benzodiazepines (used for hypnotic effect) and derivatives (zolpidem and zopiclone), carbamates and H1-antihistamines (doxylamine).

Results: In 2006, 38 (3.0%) "chronic consumers" have been compared to the 1,146 (91.2%) "non consumers" of hypnotics. We found no significant difference in QoL evolution between 2001 and 2006 (no significant Odds-Ratio for each improvement or deterioration compared to non-evolution) between these two groups for all dimensions studied: "Sleep", "Emotional reactions", "Energy" and "Social isolation".

Conclusions: This study was performed in a worker population, which is a younger population than the older patients most frequently included in hypnotic drugs use studies. After adjustment for many confounding factors, and despite the limits of our study, our results suggest that chronic treatment with hypnotics does not seem to be justified by an improvement of the QoL of a population of chronic users.

Reference 1 Marquie, JC, Jansou P, Baracat B, Martinaud C, Gonon O et al. Ageing, health and work: overview and methodology of the VISAT prospective study. *Le Travail Humain* 2002;65(3): 243–260.

925. National Trends in Antipsychotic Medication Use for Non-Psychotic Depression

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Background: Several antipsychotic medications (APMs) have recently received FDA approval for adjunctive treatment of depression.

Objectives: To estimate national trends and patterns in the use of APMs for the treatment of adult non-psychotic depression.

Methods: We analyzed National Ambulatory Medical Care Survey (NAMCS) data (1998–2009) focusing on trends and patterns in APM treatment in visits in which depression was diagnosed. NAMCS yields nationally representative estimates of visits to US physicians in office-based practice. Visits with diagnoses for established APM indications (schizophrenia, bipolar disorder, psychotic depression), visits of patients < 18 years, and visits without an active prescription for an antidepressant were excluded. Data were weighted to account for the complex NAMCS sampling design. Time trends and patterns in visits with APM treatment were examined using multivariate logistic models. Survey year was transformed to yield an associated odds ratio representing the change in the odds of APM use across the entire 12-year study period.

Results: Of 7,821 visits met our inclusion criteria. Weighted to the national US population this represents an estimated 206 million visits of which 7.8% included an APM. Over the study period, APM use rates increased from 5.3% (98–99) to 12.1% (08–09), with a multivariate-adjusted odds ratio (AOR) for time–trend of 2.15 (95%

CI, 1.52–3.06). The largest corresponding increases occurred among visits by males (AOR 3.20 [1.84–5.59]), patients >65 years (AOR 3.18 [1.05–9.61]), and patients without concurrent mental health conditions (AOR 2.67 [1.48–4.81]). For the entire study period, APM use rates were higher in psychiatrist visits (AOR 3.50 [2.49–4.92]), visits covered by public insurance (AOR 3.18 [2.45–4.14]) and visits with major depressive disorder (AOR 1.51, [1.20–1.90]), and lower in visits by Caucasians (AOR 0.62 [0.42–0.90]) and patients >65 years (AOR 0.68 [0.47–0.97]).

Conclusions: Between 1998 and 2009, APM treatment of non-psychotic depression substantially increased in US office-based medical practice. This trend represents a mainstreaming of APM use for a large patient population who has historically had low rates of APM treatment.

926. Mapping the Pro-Arrhythmic Risk of Antipsychotics: Combining Adverse Drug Reactions with Drug Utilization Data across Europe

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Background: This pilot study, within the ARITMO project, evaluated the pro-arrhythmic risk of antipsychotics (APs: ATC group N05A, excluding lithium) by analyzing the FDA Database (FDA_AERS) and European drug utilization data (15 countries).

Methods: Cases of QT prolongation and Torsades de Pointes (TdP) associated with APs were retrieved from the FDA_AERS (2004–2010). APs with unexpected signals were defined by disproportionality (Reporting Odds Ratio, ROR, with 95% CI > 1, cases > 3) and checking in Arizona_CERT (www.azcert.org). Consumption data (2006–2010) were provided from administrative databases from 15 European countries through health authority, health insurance personnel and EuroDURG members. Data were expressed as DDD/TID. Utilisation data was re-validated with data providers to enhance its accuracy.

Results: Thirty-one APs were reported in 1,467 cases of TdP/QT prolongation: 21 generated disproportionality, with 10 unexpected signals: amisulpride (ROR = 17.9; 95% CI = 11.9–26.9), aripiprazole (1.4; 1.1–1.9), bromperidol (88.5; 37.3–210.0) chlorprothixene (9.4; 3.5–25.5), cyamemazine (6.3; 3.5–11.4), fluphenazine (7.0; 3.5–14.1), levomepromazine (4.6; 2.1–10.4), olanzapine (3.7; 3.2–4.2), prothipendyl (5.5; 6.8–35.5) and zuclopenthixol (12.2; 5.4–27.8). In all countries, AP use was stable or increased from +0.11 DDD/TID (Norway) to +24.08 (Serbia). Except in Serbia, the atypical/typical ratio increased. There was variable utilization in 2010, from 5.60 (Lithuania) to 20.17 (Serbia). The mean use of APs with unexpected signals ranged from 1.72 (Estonia) to 5.45 (Slovenia). Olanzapine was stable, but peaked 2.9 in Norway. Aripiprazole increased, but no use in Serbia. Fluphenazine was substantially used only in Serbia (3.77 in 2010).

Conclusions: Differences in AP use among countries imply different levels of risk; however less variability in overall utilisation than seen with PPIs and statins. The use of atypical APs is typically growing. Aripiprazole should be closely monitored by regulators, due to its steadily increasing utilisation in most countries; fluphenazine is a specific concern in Serbia.

927. Medication Use and Comorbid Diseases in a Multiple Sclerosis (MS) Population: Electronic Health Record-Based Data

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Background: MS is the most common cause of neurologic disability in young adults, with a peak age of onset between 20 and 40 years. Data on prevalence and treatment patterns in U.S. populations has typically been based on claims data. Clinic-based data from electronic health records (EHRs) may provide complementary estimates of treatment and disease patterns.

Objectives: To describe medications used and comorbidities for MS patients as documented in the EHR for a large multi-payor health system in order to learn more about current prescribing and patient characteristics.

Methods: Geisinger Health System (GHS) is a multi-payor delivery system offering healthcare services to residents of 31 of 67 counties in Pennsylvania with 1.5 million patient visits per year and an outpatient EHR since 1996. Using the EHR, we identified patients with an MS diagnosis and at least one prescription order for an MS drug, and queried all medications and ICD-9 diagnosis codes from inpatient/outpatient encounters from 2004 to 2010 to describe the distribution of drugs used and comorbidities diagnosed before and after MS treatment.

Results: We identified 1,603 patients (22% male, 98% Caucasian, mean age 44) with a mean observation time of 30 months with an MS diagnosis (range 6–51 months). The most common initially-ordered MS drug was Copax-

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one (46%), followed by Avonex (24%), Betaseron (18%), Rebif (11%) and Tysabri (2%), with 394 patients (25%) switching drugs during the period. Most commonly prescribed non-MS drugs were antidepressants (65% of patients), corticosteroids (59%), analgesics-narcotic (49%), anticonvulsants (47%) and skeletal muscle relaxants (47%). Most common comorbid diagnoses prior to the first MS diagnosis were: hyperlipidemia (10%), hypertension (9%), arthritis (9%), malignancy (7%), and burning/numbness (5%). Most frequent new-onset diagnoses following an MS diagnosis were hyperlipidemia (13%), arthritis (12%), malignancy (11%), hypertension (10%) and insomnia (4%).

Conclusions: Clinic-based, multi-payor EHR data is a valuable source of evidence to complement claims databases when characterizing MS patients' treatment and disease characteristics.

928. Long-Term Effects of Regulatory Warnings and Increased Media Coverage on Paroxetine and Other SSRIs Use

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Background: In the periods 2003–2004 and 2007–2008 the regulatory banning of selective serotonin re-uptake inhibitors (SSRIs) in pediatrics and young adults because of concerns regarding suicidality coincided with negative media coverage.

Objectives: We analyzed trends in SSRI use in the Netherlands (NL) and the United Kingdom (UK) in the period 2000–2010 and whether trend changes could be associated with the combined and long-term effect of both warnings and media coverage.

Methods: Monthly SSRIs sales (IMS Health) were presented as DDD/1,000 inhabitants/day. Annual Dutch SSRI insurance claims data (GIP) were analyzed by age group. Trends in SSRI use were studied with time-series segmented regression analyses. Timing of trend changes was compared with the two warnings-coverage periods.

Results: Trend changes in overall SSRI use largely corroborated with the warnings-coverage periods. Growth in overall SSRI use in the UK declined from 3.9 to 0.7 DDD/month (95% CI: 3.3;4.5 0.5;0.9, respectively) before the first warning period. A small dip of -0.6 DDD/month (-1.2;-0.05) was observed in overall NL SSRI use after the first period. During the second warning period, overall UK SSRI use stabilized, whilst overall NL SSRI use slightly decreased with -0.04 DDD/month (-0.4;0.3). Stratified analyses showed a rapid decrease of -1.2 DDD/month (-2.1;-1.7) in UK paroxetine use before the first period, and a minimal change in NL paroxetine use (-0.3, -0.8;0.2). Other SSRI use, (es)citalopram, significantly increased at the same time. Significant reductions in Dutch paroxetine use were observed in pediatrics, adolescents, and young adults that started before the first period.

Conclusions: Changes in overall SSRI use (NL UK) were associated with the timing of the combined effect of media coverage and regulatory warnings. Short-term studies only provide a snapshot of the implications. We confirmed changes observed in these studies, but our long-term assessment shows that these changes were temporal, drug specific, and pronounced in young groups. The long-term growth pattern of SSRI use indicates that regulatory warnings and media coverage may slow down, but not confine SSRI use as a class.

929. Trend in Opioids Analgesic Consumption in Europe from 2002 to 2009: Impact of National Regulations

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Background: Before 2000, the under-utilisation of opioids in France led to the implementation of three consecutive national strategic plans to improve pain management since 1998. This work describes longitudinal trends in opioids use in France and in continental Europe since 2002.

Objectives: To investigate the trends in opioids consumption in Europe between 2002 and 2009.

Methods: Data collected for 30 European Countries, were extracted from the consumption reports and/or databases of the respective national authorities, and expressed in DDD/1,000 inhabitants/day (DID). Total opioids consumption (N02A) and utilization of selected substances (morphine, oxycodone, fentanyl, codeine, dextropropoxyphene and tramadol) were investigated. Moreover, information on the national opioids prescription and/or delivery regulations and their eligibility for reimbursement was also collected.

Results: Data collected were mainly represented by sales data. France was the largest consumer of opioids in 2002–2009 (about 50 DID), but this use was mainly represented by dextropropoxyphene (53.9% of total consumption in 2009 (24.7/44.7 DID) and up to 73.3% (42.6/58.1 DID) in 2005). However, the consumption of

dextropropoxyphene decreased in all countries since 2005. During the observed period, the total consumption of opioids (N02A) showed a slight increase. The consumption of morphine was stable or decreased slightly in all countries except in the UK (1.03 DID in 2005 to 1.19 in 2009 [+70%]). The utilization of fentanyl increased in most countries, in particular in Iceland (1.7–2.7), which was the largest user.

Conclusions: Levels and profiles in opioids utilization are varying extensively among European countries. In France, the amount of opioids used was mainly explained -up to 2010- by the significant contribution of dextropoxyphene containing medicines. As a consequence of definite withdrawal in March 2011, substantial changes in opioids consumption patterns are expected. The possibility for a transfer of prescribing to products with higher dependence and/or abuse potential or with unfavorable safety profile need to be closely monitored.

930. Prescribing Pattern of Psychotropic Substances in a Nigerian Neuro-Psychiatric Hospital

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Background: Psychiatric disorder accounts for more morbidity than is often recognized. In developing countries, experience has shown that there are diverse patterns of psychotropic drug prescription, the commonest being polyphamacy.

Objectives: To determine the prescription pattern of psychotropic drugs and to asses rational prescribing of these drugs in Neuro-psychiatric Hospital Yaba.

Methods: The study was carried out at the pharmacy department in the Federal Neuro-psychiatry Hospital, Yaba, Lagos. Fifty prescriptions were systematically sampled for each month for a period of 1 year (January to December 2007), giving a total of six hundred prescriptions. Data was collected using standard prescription encounter sheets.

Results: About 35.49% prescriptions contained at least an injection. Of 86.50% prescriptions contained antipsychotic drugs, other psychotropic drugs included antidepressants (27.50%), mood stabilizers (22.83%) and sedative/hypnotics (8.50%). Other drugs included anticholinergics (67.33%), analgesics (3.67%), antibiotics (3.67%), antihypertensive (11.67%), antihistamine (0.08%), antimalarials (4.50%), and haematinics (36.67%). Of 46.62% of prescriptions contained only one antipsychotic drug and 16.38% contained at least three antipsychotic drug combinations. Chlorpromazine (49.32%), Fluphenazine (32.18%), Trifluoperazine (32.76%), were the three most frequently prescribed typical antipsychotic while Clozapine (1.15%), Olanzapine (0.96%) and Risperidone (5.97%) were the most frequently prescribed atypical antipsychotics

Conclusions: This study has shown to a large extent a fairly rational prescribing pattern of antipsychotics in the Federal Neuropsychiatric Hospital Yaba, Lagos, Nigeria. However, most psychiatrists in this hospital induge in polypharmacy. Since antipsychotic polypharmacy is a widely prevalent practice without any robust evidence to back it up, more studies are needed before this practice can be justified on empirical grounds. Furthermore, prescription of drugs in generics is poor and this needs urgent attention as it may alter rational dispensing of drugs especially when the prescribed drugs are not in stock.

931. Utilization of Prescription Sedative Hypnotics in Patients with and without Insomnia Diagnosis

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Background: Sedative-hypnotic drugs are widely used to treat sleep disorders but it is unclear how their utilization varies by drug and patient diagnosis.

Objectives: To describe utilization patterns for sedative-hypnotic drugs in patients with and without a claim for insomnia.

Methods: This study was a cohort analysis of sedative-hypnotic utilization in the US-based Marketscan commercial healthcare claims database for 2008–2010. Patients included those with and without an ICD-9 code for insomnia who were treated with sedative-hypnotics including zolpidem, zaleplon, eszopiclone, short-acting benzodiazepines (alprazolam, lorazepam) and diazepam. Outcomes included mean and median number of prescriptions filled, duration between refills, and switching patterns over 1 year follow-up. All analyses were calculated with 95% confidence intervals.

Results: A substantial proportion of sedative-hypnotic use (55–92% depending on the drug) is in patients without a formal insomnia diagnosis. Across all drugs evaluated, the mean number of prescriptions per patient was consistently higher in those with than without an insomnia claim. For example, in those with prescriptions for zolpidem, patients with an insomnia claim received a mean of 4.8 (95% CI 4.76–4.81) prescriptions within a year while those without an insomnia claim received 2.8 (95% CI 2.82–2.84). Similarly the duration between refills was lower for those with than without an insomnia claim; for zolpidem, the median number of days between refills was 43.5 and 57.7, respectively. Patients with insomnia claims were more likely than those without insomnia claims to switch from one sedative-hypnotic drug to another (26.7% vs. 9.4%). The number of days between prescriptions also varied by drug, irrespective of insomnia diagnosis. Eszopiclone, zolpidem and diazepam had a shorter median num-

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ber of days between refills than short-acting benzodiazepines or zaleplon (44, 51, 52, 59 and 60 respectively).

Conclusions: Drug utilization in users of sedative-hypnotics varies by diagnosis and drug. Those with claims for insomnia receive drug for longer periods of time and with less time between refills than those without documented insomnia diagnoses.

932. Clinical and Cost Effectiveness Analysis of Post-Operative Analgesia

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Background: Review of medicine utilisation data highlighted variation in oxycodone use across two hospital sites within NHSGGC. Morphine is recommended as the first line opioid treatment for acute pain; with oral oxycodone restricted to where morphine is ineffective or not tolerated.

Objectives: To compare the clinical and cost effectiveness of postoperative analgesic regimens following elective primary hip and knee arthroplasty in the standard clinical setting.

Methods: A convenience sample was selected. Data collection was restricted to patients who had primary arthroplasty. Exclusions included patients transferred to higher level care or those with opioid dependence. Opioid consumption, pain scores, physiotherapy interventions and discharge were extracted. Adverse events were noted but causality was not formally assessed.

Results: Fifty patients were recruited; 19 were treated with intravenous morphine patient controlled analgesia (PCA); 23 with oral oxycodone and eight with other analgesic regimens. Comparison was restricted to PCA and oxycodone groups. The median (range) total opioid consumption (parenteral morphine equivalent [PME]) was higher in the oxycodone group (88 mg [29–192]) compared to the PCA group (43 mg [6–197]). Of 53% of patients in the PCA group received an intraoperative spinal opiate compared to 9% in the oxycodone group, which was not included in the calculation of PME. Patients in the PCA group experienced a higher incidence of uncontrolled pain episodes in the first 24 hours after surgery compared to the oxycodone group (2.5 vs. 1.2 episodes/patient). The requirement for supportive medication to manage adverse effects associated with opioids was low. Time to achieve physiotherapy goals was not different in either group. The median length of stay and overall cost (drug and bed costs) was similar in both groups.

Conclusions: Pain control in the first 24 hours after surgery appears to be better in the oxycodone group. Differences in analgesic effect were not sustained. Patients receiving oxycodone are exposed to a higher overall opioid consumption and the dosing schedule should be reviewed. More accurate comparison of consumption and cost would require absence of spinal opiates.

933. Impact on Physician Prescribing Practices of a Computerized Reminder for Biological Surveillance in Antipsychotic Therapy

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Background: Glucose or lipid dysregulation and arrhythmia/QTc-interval prolongation are well-known risks of antipsychotic (AP) therapy. Internally-developed guidelines in our hospital recommend that assessment of serum potassium (K), serum triglyceride (T), and fasting blood glucose (G) levels be ordered concomitantly to any AP prescription at the time of patient admission.

Objectives: The aim of the study was to evaluate the impact on physician prescribing practices of the intervention that consisted of embedding a reminder of the biological surveillance recommendation in the computerized physician order entry system of the hospital. This reminder was displayed online at the time of any AP order.

Methods: 1-day cross-sectional reviews of all inpatient medical records were used to evaluate the prevalence of K, T, or G determination at patient admission. These reviews were performed 6 months before the intervention (D0), and 6 months (D1), 18 months (D2), 24 months (D3), and 36 months (D4) after the intervention.

Results: The number of patients receiving AP therapy at admission was, respectively, 160, 184, 162, 161, and 157 on D0, D1, D2, D3, and D4. In these patients, assessment of K, T, and G levels at admission increased over the study period, respectively, from 30% of the patients on D0 to 72% on D4, from 7% on D0 to 31% on D4, and from 30% on D0 to 69% on D4 ($p < 0.01$ for either biological parameter). Over the study period, the intervention was associated with significant trends (χ^2) to: (1) a decreased use of APs at risk of QTc-prolongation (from 63% of the patients on D0 to 40% on D4, $p < 0.01$); (2) a decreased use of AP polypharmacy (from 43% of the patients on D0 to 20% on D4, $p < 0.01$); and (3) and an increased use of atypical AP monotherapy (from 27% of the patients on D0 to 47% on D4, $p < 0.01$).

Conclusions: In this study, a computerized reminder displayed at the time of AP ordering enhanced physician adherence to surveillance recommendations for some AP-related risks of side-effects. Significant changes in AP prescribing practices were concomitantly observed.

934. Prevalence and Patterns of Antiepileptic Drug-Containing Drug Combinations at Risk of Clinically Relevant Drug Interactions in a Teaching Psychiatric Hospital

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Background: In patients receiving antiepileptic drugs (AEDs), the risk of clinically relevant drug interactions (CRDIs) is common because most AEDs have a narrow therapeutic index, and the most widely used AEDs have prominent effects on drug-metabolizing enzymes.

Objectives: To evaluate the prevalence and patterns of AED-containing drug combinations (DCs) at risk of CRDIs in the adult inpatient population of a teaching psychiatric hospital.

Methods: The study consisted of a 1-day cross-sectional evaluation of all the ongoing drug regimens in the inpatient population of the hospital. The screening/rating tool for reviewing drug regimens by the pharmacy department was the knowledge base of the French Agency for Medicinal Products. Hazardous/contraindicated DCs or DCs requiring precaution for use were considered.

Results: Of the 402 inpatients present on the study day, 101 were prescribed at least 1 AED. In these AED-receiving patients, old generation AEDs (carbamazepine, phenobarbital, valproic acid, phenytoin) accounted for 75% (n = 103) of the 137 orders for AEDs. The total number of AED-containing DCs at risk of CRDIs was 65, and 41% of the AED-receiving patients was exposed to at least 1 of these DCs. Occurrence of these DCs in drug regimens correlated with the number of drugs concomitantly prescribed ($p = 0.01$). The most prevalent DC was the combination of phenobarbital with valproic acid or valpromide (n = 11). Hazardous/contraindicated DCs accounted for 28% (n = 18) of the DCs at risk of CRDIs, and two-thirds of these problematic DCs were due to the combinations of AEDs + oral contraceptives and lamotrigine + valproic acid. AED polypharmacy was founded in 26% of the AED-receiving patients and accounted for 34% (n = 22) of the DCs at risk of CRDIs (mainly, the combinations of valproic acid + phenobarbital, and valproic acid + lamotrigine).

Conclusions: AED-containing DCs at risk of CRDIs were frequently encountered in the AED-receiving patients in this study. Given the relatively high proportion of hazardous/contraindicated DCs, clinical pharmacy interventions are needed to enhance monitoring of AED therapy in our hospital.

935. Prescribing Trends of Dosulepin in General Practice: Reducing the Potential for Fatal Overdose

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Background: Dosulepin has been associated with serious ADRs and toxicity due to overdose. It has a small margin of safety between the maximum therapeutic dose and potentially fatal doses. In 2004, NICE advised only specialist-care practitioners should prescribe dosulepin. Further in 2007, the Commission on Human Medicine advised against the use of dosulepin in new patients and introduced risk-minimisation measures to reduce the potential for fatal overdose. This study investigates dosulepin prescribing patterns in general practice before and after introduction of risk-minimisation measures, to assess any impact on dosage and volume of dosulepin prescribed.

Objectives: To determine annual incidence rates for dosulepin in adults by sex, drug strength, formulation and volume issued per prescription, and to investigate the number of dosulepin associated deaths.

Methods: Annual prescribing incidence rates by sex, drug strength, formulation, and volume per prescription, were calculated with data obtained from GPRD, 2002–2010, and mortality data related to dosulepin were obtained from Office for National Statistics.

Results: From 2002 prescribing decreased by ~30,000 prescriptions per year and from 2004 the annual decrement increased to ~65,000. There was a 61% drop in the number of patients prescribed dosulepin. The number of new patients dropped from 42% of total patients in 2002 to 21% in 2010. The majority of patients were prescribed 25 mg dosulepin, but the number of prescriptions issued per patient was higher with 75 mg tablets. The quantity of tablets dispensed decreased over time. The prescription quantity of 61+ tablets exhibited the largest decline. Dosulepin was associated with 46% of antidepressant-related deaths 1993–2003. In 2004, this fell to 29% and then 11% in 2010.

Conclusions: The prescribing of dosulepin has declined since 2002, with an accelerated decline in the number of patients after 2004. A noticeable drop in the quantity of prescriptions for 61+ tablets has been seen in 2005 and 2008. These events are in line with the updated NICE guidelines and MHRA warnings. However the size of influence of regulatory action is unclear due to a declining trend prior to 2004.

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936. Serum Levels of Regulatory Peptides in Patients Treated with Antipsychotics

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Background: Patients with severe mental illness are at high risk of medical mortality and morbidity. There is an increasing evidence of metabolic syndrome (MetS) in patients on atypical antipsychotics and regulatory peptides like Ghrelin, Resistin and Leptin might be playing a key role on the pathogenesis of MetS.

Objectives: The main hypothesis of the study is to monitor the incidence of MetS in the patients receiving antipsychotic drugs and to investigate the levels of Ghrelin, Resistin and Leptin and also to evaluate the utility of various parameters such as the anthropometric measurements among study population.

Methods: *Design*: A prospective observational study was conducted among 29 patients of Department of Psychological medicine in a multi specialty hospital. *Setting*: Patients receiving antipsychotic drugs irrespective of gender were included in the study with their consent. *Exposures or interventions*: The patients were prescribed with Atypical Antipsychotics (AAPs) such as Olanzapine ($n = 29$) during the study period. *Main outcome measures*: Blood pressure, weight, height and waist circumference were measured. Blood samples were collected to assess fasting blood sugar and lipid profile as per the criteria using both descriptive and inferential statistics. *Statistical analysis*: For comparison between groups, Student's t-test regression analysis was performed.

Results: We found a significant difference in the mean of the metabolic parameters during baseline and on review as Body mass index (34.45%), Waist Circumference (31%), Systolic Blood Pressure (31.04%), Diastolic Blood Pressure (28.6%), Fasting Blood Glucose (30.9%), Triglycerides (51.9%), and High density lipoprotein (55.17%) ($p < 0.001$). Serum Ghrelin, Resistin and Leptin levels of patients with MetS were higher than the patients without MetS ($p < 0.05$, $p < 0.01$, $p < 0.001$ respectively).

Conclusions: The serum level of regulatory peptides were found higher in patients with MetS. Among them Leptin was found to be considerably increased in patients with MetS than in without. A positive correlation was found between the regulatory peptides and BMI. A higher level of leptin is an imperative indication of MetS in obese patients.

937. Risk of Suicide Attempts among Different Antidepressants in Cancer Patients

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Background: Several studies have identified increased suicide rates among cancer patients. Considering improved survival after cancer treatment, active treatment of depression should be the crucial step of preventing suicide in cancer patients. But suicide rates among different antidepressant have not been studied in a large sample of cancer population.

Objectives: This study was performed to compare the risk of suicide attempts among different antidepressants in cancer patients.

Methods: Study population had diagnosis of cancer and prescription of antidepressants after diagnosis between January 2007 and June 2008, using Korea Health Insurance Review and Assessment Database. We excluded patients if they had record of antidepressant prescription in 1 year before the index date or if they had history of suicide attempts. We classified antidepressants as tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI), and new antidepressants (NAD). Outcome was admission or visit to emergency departments for diagnosis of suicide attempts. Cox regression analysis was used to evaluate the risk of suicide attempts among different antidepressant agents.

Results: Among 32,214 cancer patient with antidepressant prescription, 663 patients (2.1%) were identified to commit suicide attemtps. Female patients were 53.7% and aged between 60 to 69 years old were 28.3%. Most common primary cancer site was liver cancer (9.2%) and tricyclic antidepressants (38.6%) were commonly prescribed in suicide attempt group. Single antidepresssant treatment did not significantly lower suicide attempts in cancer patients, hazard ratio (HR) of TCA being referent group, HR of SSRI was 0.99 (95% CI 0.79–1.21), and that of NAD was 0.95 (95% CI 0.77–1.17). Meanwhile, HR of combination treatment was as such, HR of TCA + SSRI group 0.58 (95% CI 0.40–0.82), SSRI + NAD group 0.62 (95% CI 0.44–0.88), TCA + NAD group 0.71 (95% CI 0.51–0.98), and TCA + SSRI + NAD group 0.54 (95% CI 0.36–0.81).

Conclusions: Combination treatment of antidepressants lowers risk of suicide attempts in cancer patients, especially TCA and SSRI group.

938. Evolution of Epileptic Seizures during 5 Years in Patients Treated with Sodium Valproate

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Background: Epilepsy is considered a major public health problem, It is the second neurological disease after migraine.

Objectives: To determine the sociodemographic, clinical and treatment of epileptics patients treated for 5 years with sodium valproate either as monotherapy or in combination and to study the evolution of seizures during the 5 years.

Methods: A retrospective study that included 54 patients followed in the neurophysiology department of the hospital specialties of Rabat and the neurology department of the hospital Instruction Mohammed V in Rabat.

Results: The mean age of patients was 27 years and 7 months. We had a slight female predominance (53.9%). Most patients came from Rabat and Salé. Of 42.60% of patients were enrolled in high school, patients who had no profession have shown 57.41%. Only 7.41% of patients had a history of epilepsy. The majority of patients (85.18%) benefited from the electroencephalogram, the mean age at onset of seizures was 12 years and 8 months. A predominance of generalized seizures were noted, with 79.63% against 20.37% of partial seizures. Juvenile myoclonic epilepsy type of epilepsy was the most dominant with 35.18%. Sodium valproate was used in 87.04% as monotherapy and in combination with other antiepileptic drugs in 12.96%.

Conclusions: Sodium valproate decreased the number of seizures for 5 years, primarily generalized tonic-clonic seizures, this drug is prescribed in cases of juvenile myoclonic epilepsy.

939. Influence of Body Mass Index on the Choice of Therapy for Depression and Follow-Up Care

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Background: Overweight and obese people commonly suffer from depression. The impact of antidepressant drug treatment on body weight should be considered when treatment is initiated. Based on reported associations between obesity and disparities in health care, there is concern that obese patients may receive lower quality of depression care compared to normal weight patients.

Objectives: To investigate whether there is evidence that a patient's body weight is considered when initiating treatment with antidepressant medications and/or psychotherapy. We also investigated whether patients with obesity were more or less likely to receive appropriate duration of depression treatment and receive an appropriate number of follow-up visits after initiating treatment.

Methods: Adults with a diagnosis of depression between January 1, 2006 and March 31, 2010 who had 1+ new episodes of an antidepressant medication and/or psychotherapy were eligible. Medication use, encounters, diagnoses, height, and weight were collected from health plan databases. We modeled receipt of the different therapies (medication and psychotherapy) by BMI and BMI trajectory during the 9-month prior to initiation of therapy using logistic regression models that accommodated correlation within provider and adjusted for covariates. We modeled BMI via a restricted cubic spline. Fluoxetine was the reference treatment option in the medication models.

Results: Lower BMI was associated with greater use of mirtazapine, and a declining BMI prior to treatment was associated with greater odds of initiating mirtazapine and paroxetine. Higher BMI was associated with greater odds of initiating bupropion even after adjustment for smoking status. Obese patients were less likely to receive psychotherapy and less likely to receive appropriate duration (180-day) of depression treatment compared to normal weight subjects.

Conclusions: Our study provides evidence that BMI is considered when choosing therapy but associations were weak. Our results should prompt discussion about recommending and choosing depression treatment plans that optimize depression care and weight management concurrently. Disparities in care warrant additional research.

940. Prevalence of Medication Use for Somatic Disease in Hospitalized Psychiatric Patients

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Background: Psychiatric patients use medications both for their psychiatric condition and also for treating somatic diseases or somatic adverse effects of psychotropic medicines. To assess whether psychiatric patients are optimally treated for their somatic diseases, we need to measure what the prevalence of use of medication intended for somatic disease is.

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Objectives: To estimate the prevalence of medication use for somatic disease in hospitalized psychiatric patients and changes during 2006–2010.

Methods: Cross-sectional study in hospitalized psychiatric patients. Medication use for somatic disease on ten prevalence points between 2006 and 2010 was investigated. The prevalence was stratified by gender, age, psychiatric medication class and the number of different psychiatric medication classes used. Prevalence for different classes of medication, and the average number of somatic medication received per patient were also estimated.

Results: The prevalence of medication use for somatic disease increased from 68.0% in 2006 to 76.7% in 2010. The average number of medications used for somatic disease increased from 3.4 per patient in 2006 to 4.2 in 2010. Approximately one-third (34.3%) of the patients received ≥3 medications intended for treating somatic disease in 2006 which increased to 46.2% in 2010. In 2010, the prevalence of medication use for somatic disease was highest for analgesics and antirheumatics (33.9%), acid and bowel related medication (25.6%) and anticholinergic medication (24.0%). Medication use for somatic disease was highest in patients ≥60 years (95.3%), patients treated with more than one psychiatric medication class (87.2%) and patients treated with mood stabilizers (90.6%).

Conclusions: Somatic medication use is high in hospitalized psychiatric patients. Co-use of psychiatric and somatic medications for somatic disease can lead to adverse effects, drug/disease or drug/drug interactions and inappropriate dosing. Caregivers should be aware of the consequences when use of several medications are combined which needs to be monitored and managed to improve their effectiveness and safety.

941. Comparative Evaluation of Two Drug Interaction Screening Programs in 84625 Psychiatric Inpatients

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Background: Clinical Decision Spport Software (CDSS) solutions can effectively identify drug interactions. However, comparative information regarding performance of different CDSS in clinical routine settings is limited.

Objectives: We aimed to develop solutions for mass analysis of drug interactions with CDSS and to compare the performance of different CDSS using large real-life prescription datasets.

Methods: We developed customized solutions for patient-level mass analysis of drug prescriptions for two CDSS, MediQ and ID PHARMA CHECK. These were applied to a cross-sectional collection of prescription data from 84,625 psychiatric inpatients collected through the international AMSP program. Identified interactions were reclassified according to the Zurich Interaction System (ZHIAS), a multidimensional classification that incorporates the Operational Classification of Drug Interactions (ORCA).

Results: MediQ generated a total of 270,484 interaction alerts, accounting for 6,133 unique combinations. Of 198 of those were classified as high danger, 2009 as average danger, and 3926 as low danger. ID PHARMA CHECK issued 157,469 alerts and detected 5,394 unique combinations assigned to one or several of 14 risk and management categories. Altogether both CDSS issued alerts relating to 9,379 unique interacting drug combinations, but only 2,148 were identified by both programs. The proportion of overlapping alerts increased with higher danger rating for both CDSS; it was also significantly higher for (provisionally) contraindicated combinations, according to ORCA. MediQ demonstrated higher sensitivity and better correlation of interaction grading with ZHIAS, but ID PHARMA CHECK had better specificity regarding clinically relevant alerts.

Conclusions: Overlap was significantly higher for the detection of (provisionally) contraindicated interactions between the two CDSS. For both CDSS only a small proportion of all identified interactions appeared clinically relevant according to ZHIAS.

942. Does Lifting an Administrative Restriction on Antidepressant Drug Prescribing Influence Treatment Patterns?

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Background: Drug reimbursement rules were changed in Iceland on March 1, 2009, lifting restrictions on dispensing of Selective Serotonin Re-uptake Inhibitors (SSRIs). After the change the amount of dispensed SSRI could cover 3 months, as opposed to 1 month prior to the change.

Objectives: To investigate the influence of reimbursement change on the incidence of use and early discontinuation patterns of antidepressant treatment.

Methods: This was a nationwide drug utilization study. The study population included new antidepressant users (no dispensing 12 months prior to index date) 18–69 year old from the Icelandic Medicines Registry who initiated antidepressant use between 1.3.2006 and 28.2.2010. The

study population was split into four 12-month study cohorts, three comparison cohorts (2006, 2007 and 2008) and one intervention cohort (2009) after the change. Incidence rates (per 1,000 inhabitants) by age, gender and type of antidepressant were measured. Early discontinuation (filling a single prescription) was measured as a percentage of new users in each cohort by age, gender and type of antidepressant. Incidence rate ratios (IRR) with 95% confidence intervals (CI) were used to compare incidence rates. Binary logistic regression was used to estimate odds ratios (OR) with 95% CI for early discontinuation.

Results: The overall incidence rate decreased from 33.10 to 28.71 per 1,000 (IRR 0.87; 0.78–0.97) from the 2006 to the 2009 cohort but the incidence rate for the SSRIs did not change over the period. The incidence of dispensing a 3-month dose per prescription increased from 5.49 to 13.82 per 1,000 (IRR 2.05; 1.87–2.24) from the 2006 to the 2009 cohort. Overall early discontinuation increased from 33.3% to 36.2% (OR 1.13; 1.02–1.25) and for the SSRIs from 30.02% to 34.1% (OR 1.19; 1.06–1.33) from the 2006 to the 2009 cohort.

Conclusions: The reimbursement change did not seem to affect the SSRIs incidence rates. However, early discontinuation increased following the change. Other factors, such as a financial crisis in Iceland might have influenced prescription fill patterns. The results suggest that it might be clinically more beneficial to dispense smaller doses to new users.

943. Multiple Sclerosis Treatment Patterns: A US Insurance Claims Database Study

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Background: Several drugs are indicated for the treatment of multiple sclerosis (MS). Though national recommendations for treatment are in place, the decision to begin, switch or stop MS therapies are complex and vary widely by physician and patient preference. Few population-based studies have been reported on the pattern of use of MS medications.

Objectives: To describe the proportion and pattern of initiating, switching, and stopping medications indicated for the treatment of multiple sclerosis in patients enrolled in a large US claims database.

Methods: The source population consisted of 110,349 subjects diagnosed with MS and enrolled in a US health insurance database for at least 12 months between 1/1/2004 and 6/30/2011. The analysis was restricted to persons with a first diagnosis of MS in 2008, at least 12 months and 24 months of continuous enrollment prior to and after diagnosis respectively, continuous pharmacy benefits for 24 months after diagnosis, and no report of MS therapy prior to diagnosis. The pattern of medication initiation, discontinuation, and re-initiation was quantified among the eligible MS patients through 12/31/2010. Therapy discontinuation was defined as a gap of 90 days from the expected refill date.

Results: The study population consisted of 1,727 patients diagnosed with MS in 2008 meeting the criteria for inclusion. Of 657 (38%) and 69 (4%) patients began MS therapy within 12 and 24 months of diagnosis respectively, while 1,001 (58%) remained untreated at the end of follow-up. Of 262 patients discontinued therapy prior to the end of follow-up, whereby 83 (32%) re-started, 29 (11%) restarted but later discontinued, and 150 (57%) had no reported re-start prior to the end of follow-up. Of the 464 who continued therapy with no gaps, 98 (21%) switched to an alternate treatment. The majority of patients initiated treatment with glatiramer acetate and interferon beta-1a.

Conclusions: Utilizing a large US health insurance claims database revealed that a small number of MS patients naïve to treatment initiate MS therapy in a 24-month period following diagnosis. More research is warranted to understand the drivers to treatment initiation and reasons for treatment interruption and discontinuation.

944. Antipsychotic Medication Adherence in Patients with Schizophrenia or Schizoaffective Disorder

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Background: Low adherence to prescribed medication is a widespread problem in schizophrenia and related disorders.

Objectives: The aims of our study were to determine pattern and predictors of adherence to antipsychotic medication in the early phase of schizophrenia or schizoaffective disorder.

Methods: A cohort of all patients in Sweden with a first hospitalization for schizophrenia or schizoaffective disorder during 2006 and 2007 and being <45 years old was identified from the Swedish Patient Register (n = 904). Adherence was defined as filling a prescription of an antipsychotic drug following discharge. The following potential predictors for adherence were studied in Cox regression models: sex, country of birth, metropolitan residence, educational level, age, duration of index hospitalization, history of substance use disorder, and access to antipsychotic drugs at admission.

Results: Among all patients, 53.1% (95% CI 49.9–56.4) had filled an antipsychotic prescription within 1 week from discharge, and 69.2% (95% CI 66.2–72.2) within 1 month. After 6 months, the proportion had increased to 80.2% (95% CI 77.4–82.8) but thereafter no further

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increase was observed. Prescription filling of an antipsychotic medication was primarily associated with previous adherent use of antipsychotics before admission (adjusted hazard ratio [AHR] 1.60, 95% CI 1.31–1.96, compared to no previous use of antipsychotics) and with longer duration of hospitalization (AHR 1.60, 95% CI 1.27–2.02, for 15–28 days compared to shorter hospitalization). Adherence was slightly higher in patients living in non-metropolitan areas (AHR 1.25, 95% CI 1.06–1.47) and in those without history of substance use disorder (AHR 1.40, 95% CI 1.15–1.71).

Conclusions: Among patients who fill a prescription of an antipsychotic drug after discharge, the majority do so within 1 week. Earlier use of use of antipsychotics and longer duration of hospitalization are predictors of antipsychotic medication adherence in the early phase of schizophrenia or schizoaffective disorder.

945. Triptans and Serious Cardiovascular Events: Possible Safety Signals from the FDA Adverse Event Reporting System Database

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Background: Triptans are 5-HT1$_{bd}$ receptors agonists used to treat migraine attacks. Their risk/benefit balance is considered positive in low cardiovascular (CV) risk subjects. Since the occurrence of serious CV events appear to be rare, spontaneous reports can play a relevant role to assess the safety profile of these drugs.

Objectives: To describe the CV safety profile of triptans by analysing the FDA Adverse Event Reporting System (AERS) database, with a focus on serious and unexpected adverse drug reactions (ADRs).

Methods: Reports submitted to FDA AERS from 2004 to 2010 were retrieved. Suspected and interacting drugs were mapped by anatomical therapeutic chemical (ATC) code. After duplicate removal, a case/non-case analysis was performed: cases were all reports with at least one ADR included in the MedDRA System-Organ Classes "Cardiac disorder" or "Vascular disorders", whereas non-cases were all reports other than cases. Co-reported CV drugs (ATC group C) were used as a rough proxy of CV risk and Mantel-Haenszel adjusted Reporting Odds Ratio (adj.ROR) with 95% confidence intervals (95% CI) were calculated for all levels of MedDRA hierarchy.

Results: On a total of 2,131,688 reports, 7,808 concerned triptans. Cases were 2,593 among triptan reports and 665,940 for all the other drugs. Sumatriptan was listed in 62.6% of triptan cases. The adj.ROR values yielded numerous disproportionality signals at each MedDRA level although regarding four main groups of specific disorders included in the following High Level Group Terms: Coronary artery disorders (adjROR = 2.00; 95% CI 1.85–2.16), Cerebrovascular and spinal vascular disorders (3.55; 3.27–3.87), Aneurysms and dissections non-site specific (3.45; 1.99–5.86), Vascular malformations and acquired anomalies (2.36; 1.19–4.51).

Conclusions: Our findings highlight possible unexpected associations and suggest the existence of a rare subjective susceptibility to triptan vasoconstrictive effect that, independently from CV risk factor, could lead to serious and potentially fatal ADRs. A number of published case-reports of serious ischemic ADRs in patients without CV risk factors support our hypothesis.

946. The Use of Antidepressants and the Risk of Interstitial Lung Disease (ILD) in Patients with Respiratory Disease: A Nested Case–Control Study

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Background: The use of antidepressant drugs (ADs) is growing and some anecdotal reports suggest an increased risk of interstitial lung disease (ILD) with these medications.

Objectives: To estimate the risk of ILD associated with ADs use, according to their potency in reducing serotonin reuptake.

Methods: A nested case–control analysis was performed within a cohort of 1,410,211 patients (18 years or older) treated for respiratory conditions during 1990–2005, identified using the Quebec health insurance databases and followed until 2007. Cases of ILD were defined using ICD-9 and the ICD-10 codes in records of hospitalisations and physician visits. Up to 10 controls per case, matched on age, gender, month and year of entry into the cohort, and at risk on the date of ILD diagnosis, were randomly selected from the cohort. Conditional logistic regression was used to compute odds ratios of ILD which, for the time-matched nested case–control design used here, provided an accurate estimate of the adjusted rate ratio (RR) and the related 95% confidence intervals (CI) of ILD associated with the use of the different exposure strata to ADs.

Results: Within the cohort of over 1.4 million patients, 6,665 cases of ILD were identified (incidence rate = 8.1/10,000 per year). The adjusted RR of ILD associated with current antidepressant use was 1.08 (95% CI: 0.99–1.80). There was a trend to increasing risk of ILD with a higher potency in reducing serotonin reuptake: from low potency (RR = 0.87; 95% CI: 0.71–1.06), intermediate (RR = 1.15; 95% CI: 0.73–1.33) and high potency (RR = 1.17;

95% CI: 0.97–1.41). Among users of intermediate and high potency ADs, the risk of ILD was found to be higher with the highest cumulated dosage during the last year of follow-up (RR = 1.22; 95% CI: 1.01–1.48).

Conclusions: Although the excess risk of ILD in users of ADs appears minimal, there may be a small excess in risk associated with higher cumulative doses of intermediate and high potency inhibitors of serotonin reuptake.

947. A Comparison between the Standard Self Controlled Case Series Design and a Modification To Account for Events That Censor the Observation Period

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Background: An important assumption of the self controlled case series method relates to the observation period of patients as this period should end independent of the timing of the event of interest. Use of the standard self controlled case series when violating this assumption, for instance in the extreme example of a fatal event, could potentially lead to unpredictable "censoring" bias.

Objectives: The objective of the current study was to use a recently developed extension of the self controlled case series method to investigate the effect of exposure to antipsychotic agents on the risk of myocardial infarction (MI) and to compare the outcome to the result of a standard self controlled case series method.

Methods: Our study population included 3,163 adult patients with a first recorded occurrence of MI and a first recorded prescription for a typical or atypical antipsychotic agent during the up to standard patient follow-up period in the General Practice Research Database (GPRD). Relative incidence ratios were calculated by comparing the rate of MIs experienced during high risk periods with the rate of events during baseline time, using Poisson regression. A mixed exponential and Weibull model was used to model the density of age at the end of observation.

Results: The follow-up time of 7% of all patients ended within 60 days of their MI. Using the modified self controlled case series design there was strong evidence of an increase in risk of a recorded MI during the first 30 days after the prescription of antipsychotic agents, both typical (rate ratio [RR] 2.07, 95% CI 1.58–2.72) and atypical (RR 1.58, 95% CI 0.89–2.80). Results using the standard case series design were similar to results of the modified design: Typical (RR 1.98, 95% CI 1.51–2.60) and atypical (RR 1.57, 95% CI 0.89–2.78).

Conclusions: Event dependent censoring did not result in any large bias in this study. The results of the modified self controlled case series design were similar to the results of the self controlled case series study when not adjusted for non-random censoring of the follow-up time.

948. Patterns and Determinants of Anti-Inflammatory Drug Use among Users of Antidepressants between 1997 and 2006 in Denmark

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Background: Recently both increased and decreased antidepressant treatment response of concomitant use of antidepressants (ANDs) and anti-inflammatory drugs (AID) have been reported. Though ANDs and AIDs are both frequently used, little is known about the prevalence and determinants of AID consumption in users of ANDs in an unselected population.

Objectives: Describe patterns of AID consumption among users of ANDs.

Methods: Population-based linkage study of medical and socio-demographic registries in Denmark of all starters of AND (ATC-code N06A) between 1997 and 2006 within a 25% sample of the Danish population. The date of AND prescription was termed index date, an exclusion criterion was AND use in the year before index. Prescriptions for AIDs (ATC-code M01A and N02B) were identified during the year prior to and after index, as well as somatic and psychiatric comorbidity and socio-demographic factors before index. AIDs were grouped as ASA (e.g., aspirin), NSAIDs (e.g., ibuprofen), non-selective COX-inhibitors (e.g., diclofenac) and selective COX-Inhibitors (e.g., celecoxib). Logistic regression was performed to identify determinants of AID use.

Results: Of 174,845 individuals started a first episode of AND treatment. Selective Serotonin Reuptake Inhibitors (SSRI) (70.9%) and Tri-Cyclic Antidepressants (TCA) (13.4%) were the most frequently prescribed ANDs, Citalopram being the most popular (41.3%). During the year after AND initiation, 70,370 (40.3%) overall and 36.8% of SSRI and 61.3% of TCA users redeemed at least one prescription for an AID. The pattern of AIDs among SSRI and TCA users was 18.7% and 30.7% for ASA, 16.2% and 30.2% for NSAIDs, 9.8% and 20.9% for non-selective and 2.6% and 6.3% for selective COX-Inhibitors, respectively. Adjusted for AID use prior to AND treatment, determinants for AID use after AND treatment initiation were age 30–60 years, female gender, low education, use of TCA and musculoskeletal disease. Previous hospitalizations with schizophrenia or depression lowered the risk for receiving AIDs. Interestingly, AID use increased from 1997 to 2006, especially among TCA users.

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Conclusions: We found a high prevalence of ASA, NSAID and non-selective COX-inhibitors use in users of ANDs. The next step will be to model anti-depressive treatment response using a combination of registry and clinical data and investigate the effect of AIDs on SSRI treatment response.

949. Use of Antipsychotics and Risk of Cerebrovascular Events in Schizophrenic Patients: A Nested Case–Control Study

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Background: Recent concerns have been raised regarding an increased risk of adverse cerebrovascular events associated with antipsychotics use in patients with dementia. However, the link between the use of antipsychotics and increased risk of cerebrovascular events among schizophrenic patients has been questioned, and no study has been done in Asian population.

Objectives: This nested case–control study assessed the association between antipsychotic use and cerebrovascular adverse events among schizophrenic patients.

Methods: Using Taiwan's National Health Insurance Research Database (NHIRD), we identified 9,715 newly diagnosed schizophrenic patients between 2001 to 2009. Within the schizophrenic cohort, 386 cases of cerebrovascular events and 772 matched controls (1:2 ratio) were further identified. Conditional logistic regression models were used to examine the association between the use of antipsychotics (timing, duration, and type) and risk of cerebrovascular events.

Results: Current users of antipsychotics were associated with a twofold risk of stroke (adjusted OR 1.94, 95% CI 1.11–1.39, $p = 0.02$) as compared to non-users. Among current users, patients who used antipsychotics < 15 days (adjusted OR 9.41, 95% CI 3.08–28.71, $p < 0.01$) and 16–30 days (adjusted OR 6.90, 95% CI 1.09–43.69, $p = 0.04$) were associated with an extremely high risk of stroke. The risk of stroke was greater for patients used first generation antipsychotics alone or combined use of first and second generation antipsychotics, with adjusted OR 2.75 (95% CI 1.34–5.64, $p < 0.01$) and 2.37 (95% CI 1.20–4.68, $p = 0.01$), respectively, but not in patients used second generation antipsychotic alone.

Conclusions: This population-based study extends previous evidence by documenting the increased cerebrovascular events associated with antipsychotic use in a schizophrenic cohort. A temporal association of such risk was reported in our study. Further studies are needed to assess the risk-benefit profile of first and second generation antipsychotics in this patient population.

950. Adverse Events of Cholinesterase Inhibitors: 10 Years of WHO's Vigibase Reports

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Background: Worldwide, three cholinesterase inhibitors (ChEIs), donepezil, rivastigmine and galantamine, have been used against Alzheimer's disease (AD) and associated disorders since 1997. Adverse events (AE) of ChEIs have been reported to the WHOs's Vigibase, but reports have rarely been analyzed.

Objectives: To describe trends of AE reports over time, according to country, severity, system organ class (SOC) and ChEI type, as reported to Vigibase.

Methods: All reports to Vigibase for one of the three ChEIs were included in descriptive analyses. Reporting countries were regrouped according to continent (Europe, Asia-Pacific, Africa, Latin America/Caribbean and North America). The SOCs of main interest were psychiatric (SOC = 500), gastro-intestinal (GI) (SOC = 0600), nervous system (NS) (SOC = 410) cardio-vascular (CV) (SOC = 1,010, 1,020, 1,030 plus syncope) and general disorders (SOC = 1,810). Frequency distributions were obtained for all AEs, the subgroup of severe AEs and for CV events, for each year between 1998 and 2008.

Results: Over 10 years 21,791 events for 9,069 patients were reported from 44 countries. Of 57% of patients were women and 38% men ($p < 0.001$). The median age was 78 years. Most reports came from North America (56.2%), followed by Europe (36.2%), Asia-Pacific (6.7%), South America (0.7%) and Africa (0.2%). Psychiatric AEs were most frequent (19.2%), followed by GI (16.0%), NS (15.7), CV (13.3%) and general (8.8%) AEs. All other AEs accounted for 27.0%. Most reported AEs concerned donepezil (48.4%), followed by rivastigmine (33.4%) and galantamine (18.2%). Reports of all AEs increased from 1,854 in 1998 to a maximum of 3,087 in 2001, but then decreased to reach 1,475 in 2008. There were 22 serious AEs in 1998, 1,132 in 2005 and 989 in 2008. This increase in the last 4 years was most pronounced for rivastigmine. Each year, between 10% and 15% of AEs were cardio-vascular.

Conclusions: Reporting of ChEI AEs between 1998 and 2008 followed a bell-type curve for all types of AEs, but increased for severe AEs. Cardiovascular events are lesser known AEs of ChEIs and, given their seriousness, merit further exploration.

951. Risk Factors for Carbamazepine Induced Serious Skin Reactions

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Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are extremely rare reactions, which develop due to multiple causative factors, including specific medications. Certain drugs, e.g., carbamazepine, are most commonly reported.

Objectives: To identify possible risk factors for development of SJS and TEN in carbamazepine treated patients.

Methods: We used data from the Swedish database of spontaneously reported adverse drug reactions (Swedish Drug Information System, SWEDIS). The information in a report consists of patient demographics, reported ADRs, concomitant medication and a case narrative. All reports are reviewed by clinical assessors at the MPA and a causality assessment is made. In this case–control study, we selected all patients who had been reported from 1965 to 2010 to having experienced SJS or TEN where carbamazepine was the suspected causative drug. We compared demographic, drug treatment and clinical data for these patients with those patients who had experienced any other type of ADR reported during the same time period. To test the validity of the data, we also investigated whether known risk factors for hyponatremia and SIADH, i.e., high age, female gender, high dose of carbamazepine, and concomitant treatment with SSRIs or diuretics, would be significantly different between cases and controls.

Results: Mental disorders due to alcohol were statistically significantly more common among cases than controls (34.5% vs. 8.7%, odds ratio (OR) = 5.5 [95% confidence interval (CI) 3.6–8.4], p = 3.14*10–14). Average time to onset was also shorter among cases than controls (67 vs. 127 days). Most of the known risk factors for hyponatremia and SIADH were significantly different between cases and controls.

Conclusions: In this case–control study, we identified alcohol abuse as a possible risk factor for serious mucocutaneous reactions. The possibility of an association between alcohol abuse and any type of skin reaction was determined to be unlikely as there were no statistically significant differences in factors related to alcohol abuse between patients with dermatologic ADRs other than SJS, TEN, and patients with non-dermatologic ADRs.

952. Assessment of Malignancy Risk in Patients with Multiple Sclerosis Treated with Intramuscular Interferon beta-1a: A Retrospective Evaluation Using a Health Insurance Claims Database and Postmarketing Surveillance Data

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Background: Intramuscular interferon beta-1a (IM IFNβ-1a), a multiple sclerosis (MS) therapy commercially available for over a decade, provides the unique opportunity to retrospectively assess postmarketing data for evidence of malignancy risk relative to the limited data which are available with more recently approved therapies.

Objectives: Postmarketing and claims data were analyzed to determine the risk of malignancy in MS patients treated with IM IFNβ-1a.

Methods: The cumulative reporting rates of suspected adverse drug reactions coded to a malignancy in the IM IFNβ-1a global longitudinal safety database were compared to malignancy incidence rates from the WHO GLOBOCAN database. Additionally, the cumulative prevalence of malignancy in MS patients treated with IM IFNβ 1a was compared to non-MS population controls, MS patients without IM IFNβ 1a use, and untreated MS patients using data from a large US claims database.

Results: During the postmarketing period an estimated 402,250 patients received IM IFNβ-1a. Cumulative reporting rates of malignancy in this population were consistent with GLOBOCAN incidence rates. In the claims database, 12,894 MS cases were IM IFNβ 1a users. No significant difference in malignancy prevalence was observed in IM IFNβ-1a users compared to other groups.

Conclusions: Results from this evaluation provide no evidence of an increased risk of malignancy with IM IFNβ-1a use.

953. The Risk of Glaucoma Attack in Patients Received Anticonvulsants

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Background: The risk of glaucoma attack associated with anticonvulsant use has not been clarified so far.

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Objectives: To estimate the risk of glaucoma attack in patients used different anticonvulsants.

Methods: We used the Taiwan National Health Insurance Claim Database, which contained the complete medical claims of all 23 million residents in Taiwan, to conduct a case-crossover study. All patients with glaucoma diagnosis were identified by ICD-9-CM code 365, combined with prescription of antiglaucomatous medication in one physician contact record during January 1, 2006 and December 31, 2007. Patients with glaucoma diagnosed in the year before or had secondary glaucoma were excluded. We defined the date of the first glaucoma diagnosis as index date, the 1–30 days and the 91–120 days prior to the index date as case and control period, respectively. The anticonvulsant usage history during the case period was compared to that in the control period for the same patient as a within patient matching pair. The selected anticonvulsants were classified based on the mechanism as three categories:topiramate, sodium channel blocker (SCB) and GABAergic drugs (GABA). The risk of each anticonvulsant as well as the category was estimated. The other concomitant medication associated with glaucoma were adjusted. Conditional logistic regression was used to estimate the adjusted odds ratios (OR) and associated 95% confidence interval (95% CI). Sensitivity analysis by changing the time window of the case and the control periods were carried out.

Results: A total of 125,646 cases were selected for the final analysis. Among all of the drugs, oxcarbazepine was associated with the highest and statistically significant risk of glaucoma attack, the adjusted OR (95% CI) was 1.94 (1.37–2.76). The adjusted OR (95% CI) for topiromate, SCB and GABA were 1.21 (0.72–2.05), 1.15 (1.01–1.31) and 1.18 (1.07–1.29), respectively. Sensitivity analysis showed the statistically significantly increased risk for patients receiving oxcarbazepine was consistent.

Conclusions: The increased risk of glaucoma attack in patients received oxcarbazepine was discovered which was never reported in the literature before. Further investigation would be needed to verify this observation.

954. Measuring Psychotropic Drug Exposures in Register-Based Studies – Validity of a Dosage Assumption of 1 Unit Per Day in Older Finns

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Background: Pharmacoepidemiological studies provide valuable information on the relationships between psychotropic drug use and adverse outcomes in older people. To minimize the influence of misclassification bias in pharmacoepidemiological studies, more emphasis should be given to methodological aspects of exposure assessment.

Objectives: This study evaluated the validity of a dosage assumption of 1 unit per day for measuring legend duration of psychotropic drug exposures among older people.

Methods: Using data from the Finnish Prescription Register, the study analyzed 62,320 psychotropic drug prescriptions dispensed to people aged ≥75 years (n = 52,729) in September 2009. The proportions of prescriptions in which the prescribed dose deviated from 1 unit per day were assessed for categories and subcategories of psychotropic drugs. The prescription was considered misclassified (1) if the prescribed drug was intended for "as needed" use; (2) if the prescription included a dose range, or (3) if the prescribed dose was below or above 1 unit per day.

Results: Among antidepressants, less than every fourth (23.7%) prescription was misclassified. The proportions of misclassification varied substantially across subcategories, being 13.1% for selective serotonin reuptake inhibitors (SSRIs), 25.3% for other antidepressants and 53.8% for tricyclic antidepressants. Of the benzodiazepine and antipsychotic prescriptions, 79.9% and 57.6%, respectively, were misclassified.

Conclusions: The dosage assumption of 1 unit per day is valid for measuring the legend duration of SSRI and other antidepressant exposures among older people. Among other psychotropic drugs, the dosage assumption is likely to lead to severe exposure misclassification.

955. A Cohort Analysis of the Association between Parkinson's Disease and Cancer Using the UK General Practice Research Database

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Background: Studies suggest that Parkinson's disease (PD) may increase the risk of melanoma and decrease the risk of other cancers. A proposed association between levadopa therapy and increased melanoma is unproven. This study used a dataset of 50,709 patient records from the UK General Practice Research database to analyse the association between PD and cancer and the association between levadopa therapy and melanoma.

Objectives: To compare (1) the incidence of melanoma between people with PD and people without the disease; (2) the incidence of other cancers between people with PD and people without the disease; and (3) the incidence rates of melanoma before and during levadopa treatment.

Methods: Cox regression techniques were used to compare the rates of cancer in 8,549 people with PD to the rates in 42,160 people without PD. Age, sex, smoking, alcohol, BMI and number of consultations were co-vari-

ates. Rates of melanoma before and after (1) PD diagnosis date; and (2) start of levadopa therapy were also investigated.

Results: The rate of melanoma was similar for those with and without PD (adjusted RR 1.09, 95% CI 0.68–1.76). Melanoma rates were comparable before and after (1) PD diagnosis (RR 1.05, 95% CI 0.67–1.67); and (2) starting levadopa therapy (RR 1.01, 95% CI 0.65–1.58). There was weak evidence that PD was associated with a small decrease in the rate of all other cancers overall (RR 0.93, 95% CI 0.86–1.02), and stronger evidence for reductions in the rate of lung cancer (RR 0.73, 95% CI 0.55–0.98) and prostate cancer (RR 0.74, 95% CI 0.59–0.93).

Conclusions: Our results do not suggest that PD is associated with increased melanoma and are consistent with pre-PD diagnosis results from a recent meta-analysis (OR 1.07, 95% CI 0.62–1.84). We found little evidence of increased melanoma ascertainment after PD diagnosis, however ascertainment bias may have driven contrasting results in the literature. Our results do not support case reports/warnings in prescribing information that levadopa may activate melanoma. The observed reduction in prostate cancer rate is consistent with a recent meta-analysis (RR 0.80, 95% CI 0.72–0.88).

956. Weight Gain Associated with Antipsychotics in a Naturalistic Setting: Icaro Study

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Background: Metabolic syndrome increases morbidity and mortality in patients treated with antipsychotics; weight gain in particular accounts for a higher treatment discontinuation, and worsening of physical health.

Objectives: To identify risk factors of antipsychotics-induced weight gain.

Methods: Design Follow-up study of patients treated with antipsychotic for the first time and for whatever disease (www.uva.es/estudioicaro). Setting Patients over 18 years attending community services or hospitals were included; those with body mass index (BMI) higher than 35 were excluded. Exposure Antipsychotics plus other risk factors of interest (also genetics). Main outcome measure The primary measure was weight gain, others were BMI and waist perimeter. Statistical analysis Student t-test for comparing continuous variables and the Pearson Chi-square test for comparing proportions.

Results: A total of 110 patients have been recruited so far, from these 92 (83.6%) remain in the cohort, 81 (73.6%) having completed the follow-up period of 6 months. At 6 months, body weight increased between 6 and 10.9 kg in 17.3% and more than 11 kg in 7.7% of patients (n = 52). The risk was greater in males and subjects under 55 years. At 6 months, the mean waist perimeter in men increased 5.2 cm (IC 95% 1.5–8.8). On the contrary, women older than 55 years tended to show a decrease or maintenance of initial body weight. The proportion of patients with more than 2 kg weight gain was significantly higher among those with a waist perimeter higher than 91 cm.

Conclusions: Males under 55 years with smaller waist perimeters showed a higher risk of body weight gain when treated with antipsychotics. A network of researchers and a cohort of 110 patients treated with antipsychotics have been established.

957. Preadmission Antidepressant Use and Mortality Following Atrial Fibrillation: A Population-Based Cohort Study

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Background: Atrial fibrillation (AF) is prevalent in 1–2% of the general population rising to 8% in individuals above 80 years of age. Depressive symptoms are associated with cardiovascular mortality and morbidity, but few data exist on antidepressant use and outcomes following AF.

Objectives: To assess the association between preadmission antidepressant use and mortality following first time hospital admission for AF.

Methods: This cohort study included all patients hospitalized with a first-time diagnosis of AF in Northern Denmark between 1991 and 2004. Exposure data on filled prescriptions for antidepressants, as well as use of cardiovascular drugs, cardiovascular and comorbidities, demographics, and complete follow-up for mortality were obtained from population-based medical databases. We computed 30-day and 1-year mortality. Using Cox regression we estimated hazard ratios (HRs) of mortality comparing current (prescription filled within 90 days of admission) and former antidepressant users with nonusers while controlling for potential confounding factors.

Results: We identified 33,467 patients with a first-time AF diagnosis, of whom 3,536 (10.6%) were current users of antidepressants at time of admission. The 30-day mortality was 13% among current users and 6% among nonusers. The corresponding adjusted hazard rate (HR) comparing current users with non-users was 1.6 (95% CI: 1.4–1.8). From 31 days to 1 year from admission the adjusted HR was 1.4 (95% CI: 1.3–1.6). The hazard ratios comparing former antidepressant users with non-users were 1.1 (95% CI: 1.0–1.3) for both 0–30 days and from 31 to

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365 days following admission. HRs did not vary according to type of antidepressant used.

Conclusions: Preadmission use of antidepressants is associated with increased short and long term mortality following admission with AF.

958. Risk of Suicidal Acts in New Anticonvulsant or Antidepressant Drug Users with Chronic Pain Conditions

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Background: Antidepressant and anticonvulsant drugs are often used, both on- and off-label, to treat chronic pain. Both drug classes have been associated with an increased risk of suicidality.

Objectives: To estimate the risk of suicidal events associated with the initiation of frequently prescribed anticonvulsant vs. antidepressant therapy in patients with chronic pain, i.e., gabapentin vs. tricyclic antidepressants (TCAs), and no recorded diagnosis of mood disorders or seizure.

Methods: We conducted a cohort study of patients 10 years and older in a population-based database of all British Columbia residents who initiated gabapentin or TCAs between 1996 and 2006. All subjects had recorded diagnoses of neuropathic pain, fibromyalgia, migraine, or other chronic pain conditions (back pain, osteoarthritis, rheumatoid arthritis, other arthritis, pain requiring opiates, or headache). Patients with any diagnosis of mood disorder or seizure were excluded. Suicidal events were attempted suicides (hospitalizations with an ICD-9 E-code of E950.xx–E958.xx) or completed suicides (deaths with an ICD-9 E-code of E950.xx–E958.xx or an ICD-10 code of X60-X84). PS-matching for 64 covariates was used to evaluate the risk of suicidal events associated with gabapentin compared with TCAs. HdPS-matched analyses were used to confirm adjusted findings.

Results: There was a total of 143 suicidal events: 18 in 41,108 new treatment episodes with gabapentin (mean follow-up, 100 days), and 125 in 179,339 episodes with TCA (mean follow-up, 106 days). 1:1 PS-matched analysis identified 34 suicidal events (17 events in each treatment group) in 77,512 new treatment episodes. We found no meaningful variation in the 180-day risk of suicidal events between gabapentin and TCA initiation (RR = 1.06; 95% CI, 0.54,2.08). A 1:1 HdPS-matched analysis produced consistent results (RR = 1.06; 95% CI, 0.53,2.12). Varying the follow-up period from 180 to 90 or 365 days made no important difference in the results.

Conclusions: This analysis suggests that, among patients with chronic pain conditions, there is no substantial difference in the risk of suicidal events between gabapentin and TCA initiation.

959. A Case–Control Study of Clinical Management Factors and Phenotypic Characteristics Increasing the Risk of Myocarditis with Clozapine

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Background: Despite the implementation of cardiac monitoring guidelines, clozapine-induced myocarditis continues to cause deaths in Australia, and the risk is a barrier to prescription of this effective drug for the treatment of schizophrenia.

Objectives: To identify clinical and phenotypic risk factors for clozapine-induced myocarditis.

Methods: Potential cases of clozapine related myocarditis occurring between June 1993 and November 2009 and a comparative group of controls taking clozapine for at least 45 days without cardiac disease were documented from the patients' medical records. Cases met a case definition involving clinical and cardiac-specific diagnostic features of new-onset cardiac impairment in the absence of any other plausible cause. Controls were matched to cases by psychiatric unit and by clozapine start date. Data collected included gender, date of birth, daily dose of clozapine, concurrent medication, BMI, ethnicity and smoking status. Odds ratios were calculated using logistic regression analysis without consideration for matching.

Results: Of 105 cases, with time to onset 10–33 days, and 296 controls were included in the study. In multivariate analysis, the risk of myocarditis increased 26% for each additional 250 mg of clozapine administered in the first nine days of clozapine titration (odds ratio 1.26; 95% confidence interval 1.02–1.55; p = 0.03) and concomitant sodium valproate more than doubled the risk (2.59; 1.51–4.42; 0.001). Further, each successive decade in age was associated with a 31% increase in risk (1.31; 1.07–1.60; 0.009). Nevertheless, 33 cases received < 920 mg of clozapine during the first nine days of dose titration, did not take sodium valproate and were aged < 40 years; and nine control patients received sodium valproate and more than 920 mg of clozapine in the first nine days without developing myocarditis.

Conclusions: Clozapine should be initiated by slow dose titration and sodium valproate is best avoided, if clinically feasible, during this period. All patients commencing clozapine should be monitored for myocarditis up to Day 28.

960. The Association between Antipsychotic Use and Tardive Dyskinesia, Parkinsonism and Akathisia in People with Mild Intellectual Disability

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Background: Although antipsychotics are frequently prescribed to treat psychiatric disorders and behavioral problems in people with mild intellectual disability (MID), knowledge about the prevalence of adverse effects like tardive dyskinesia, parkinsonism and akathisia is lacking.

Objectives: The aim of this study is to determine the prevalence of tardive dyskinesia, parkinsonism and akathisia among inpatients with MID and behavioral problems and to investigate the association with antipsychotic drug use.

Methods: A cross-sectional study was conducted in inpatient treatment facilities for adults with MID and severe challenging behavior in the Netherlands. Participants that gave informed consent were examined by a trained physiotherapist, using a standard protocol assessing dyskinesia, akathisia, parkinsonism and dystonia using respectively the Abnormal Involuntary Movement Scale, the Barnes Akathisia Rating Scale, the Unified Parkinson Disease Rating Scale (parkinsonism) and one separate item for dystonia. Demographic data, psychiatric diagnoses and medication data up to a year previous to the examination were extracted from the medical records. The strength of the association between antipsychotic drug use and the presence of movement disorders was estimated with logistic regression and expressed as odds ratios with 95% CI.

Results: Of the 135 included participants, 59 (43.7%) had at least one movement disorder. Frequencies of the different movement disorders were 37.0% parkinsonism, 11.9% dyskinesia, 9.6% akathisia, 0.7% dystonia. More than 85% of the participants with at least one movement disorder used antipsychotics, resulting in a statistically significant increased risk, OR = 4.4 (1.0–19.0 95% CI).

Conclusions: Movement disorders are an underestimated problem in people with mild intellectual disability. The frequent and long term use of antipsychotics in this population which often cause these adverse effects is concerning.

961. Methodologic Issues Related to an Evaluation of Opioid Abuse Deterrence in the Community

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Background: Prescription opioid abuse is a behavior associated with serious outcomes and is often linked to tampering. The FDA has approved opioid products designed to deter common forms of tampering. These opioids are often referred to as abuse deterrent formulations (ADF) in the literature, although no opioid yet has that designation in its prescribing information; substantial evidence of abuse deterrence in the community is needed. The evaluation of abuse deterrence for an ADF through long-term epidemiologic studies presents unique study design considerations and methodologic issues; and, currently, no regulatory precedent or guidance exists.

Objectives: To identify key methodologic issues for evaluating abuse deterrence in the community for ADF opioids.

Methods: We performed a systematic and critical review of epidemiology study designs and corresponding analytic methods; conducted a literature review of opioid abuse and the evaluation of abuse deterrence; consulted with key opinion leaders and experts in pain and opioid abuse; and consulted with regulatory experts, including advisors to a joint Anesthetic and Life Support Drugs and Drug Safety and Risk Management FDA Advisory Committee Meeting (October 21–22, 2010).

Results: We identified ten key methodologic issues that must be addressed in an epidemiologic evaluation of an ADF designed to assess abuse deterrence in the community. The ten methodologic issues are related to (1) study design; (2) objectives; (3) sub-populations; (4) product and method of abuse specificity; (5) population exposure; (6) choice of comparator; (7) data sources; (8) endpoints; (9) effect size (i.e., what level of abuse deterrence constitutes a public health benefit); and (10) analytic methods. For each, we present the specific methodologic issues unique to assessing abuse deterrence of an ADF; we also identify the most influential factors.

Conclusions: An epidemiologic evaluation designed to assess abuse deterrence of an ADF must identify and address several methodologic issues; and not all are equal. The two most influential methodologic issues in the design of such an evaluation are related to population exposure and effect size.

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962. Hepatotoxicity Related to New Antidepressants: A Case Non-Case Approach with Information from the Portuguese, French, Spanish and Italian Pharmacovigilance Systems

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Background: Drug-induced liver injury remains the single leading cause of drug withdrawal despite of a rigorous preclinical and clinical review process. Antidepressants have been associated with liver injury and some of them were withdrawn from the market for this reason.

Objectives: To learn the risk of hepatic damage associated with the use of new antidepressants.

Methods: A case/non-case analysis of data obtained from the Portugal, Spain, France and Italy Pharmacovigilance System databases was used. Cases were defined as reports of any hepatic damage; non-cases were reports of all reactions other than hepatotoxicity. Exposure was defined as the mention of an antidepressant in a report, either being or not being suspected of causing the reaction. For each antidepressant, the reporting odds ratio with a 95% confidence interval (95% CI) was calculated.

Results: Seventeen antidepressants were assessed for hepatotoxicity. Agomelatine was associated with hepatotoxicity in Spain (4.0 [95% CI, 2.0–8.0]) and in Italy (5.1 [95% CI, 1.7–14.0]); mianserin in France (1.3 [95% CI, 1.2–1.5]) and in Italy (5.1 [95% CI, 1.5–15.6]); and sertraline in Spain (1.7 [95% CI, 1.2–2.4]). For those antidepressants that were withdrawn from the market, nefazodone in Spain and amineptine in France, the estimates were 4.8 (95% CI, 1.7–13.7) and 12.3 (95% CI, 10.9–13.9), respectively.

Conclusions: No particular risk of hepatotoxicity was found with most of the antidepressants except for agomelatine and mianserin, also marginally for sertraline; in the case of agomelatine, it could be partially explained since this drug is subjected to a risk management plan. Information from pharmacovigilance databases of different countries may contribute to better identify risks associated with new medications.

963. Design of a Post-Marketing Study Program To Assess the Effects of a Reformulated Extended-Release Oxycodone Tablet on Its Abuse

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Background: In the US, the under-treatment of pain and prescription medication abuse are serious public health issues. Extended-release (ER) oxycodone, considered safe and effective when used appropriately, is a target of abusers. Purdue Pharma reformulated its ER oxycodone to be harder to crush and to form a gel when dissolved, while bioequivalent to the original. Beginning in August 2010, all shipments were limited to reformulated product (ORF).

Objectives: To assess the impact of a formulation change on product-related abuse, misuse, overdose and death in the real-world setting.

Methods: Study outcomes include routes of abuse and rates of abuse, clinical outcomes, and diversion. Populations of interest include occasional and daily opioid abusers, patients, law enforcement officers, adolescents and the general population. No single study can cover these outcomes and populations, so eight studies were designed. Different data sources offset the weaknesses of any one data source. Changes from before to after ORF introduction were assessed and compared to changes for comparator prescription opioids. Studies that have stable pre-introduction data were selected to understand secular trends.

Results: Studies assess changes after ORF introduction in: (1) routes of administration and rates of abuse among patients assessed for substance abuse treatment; (2) rates of opioid overdose and poisoning events, by opioid prescribed, in the Kaiser Permanente population; (3) rates of exposures reported to US poison centers; (4) rates of abuse reported in national survey; (5) law enforcement events in the RADARS® Drug Diversion Program; (6) doctor shopping in state Prescription Monitoring Programs; (7) monitoring internet chat room discussions about ORF abuse; and (8) oxycodone abuse patterns in a cohort in Kentucky.

Conclusions: Findings from all eight studies will be examined in their totality to assess the magnitude, direction and consistency of effects on outcomes. A "mosaic" of different databases and populations will be used for a comprehensive assessment interpreted with input from clinical, statistical, epidemiologic and abuse external experts.

964. Relative Risk of Myeloid Neoplasms in Patients Taking Benzodiazepines

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Background: Myeloid neoplasms (MNs) are a subset of hematologic malignancies that include myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMPD), and acute myeloid leukemia (AML). Exposure to immunosuppressant chemotherapy drugs is a known risk factor. Benzodiazepines (BZDs) are commonly prescribed drugs that affect the immune system through peripheral benzodiazepine receptors, found in many organ tissues including cells from the hematopoietic system, but there is a paucity of reliable information on BZDs and the risk of MNs.

Objectives: To estimate the effects of exposure to BZDs on the risk of MNs, by MN subtype.

Methods: We conducted a nested case–control study using the General Practice Research Database. Incident cases of MNs were identified and up to four controls were matched to each case. We categorized exposure as receipt of more than one prescription for a BZD prior to the index date compared with a referent group of "non-exposed" (those who received only one prescription for a BZD); exposed were further stratified by current or past use, number of prescriptions/duration of use, and by individual BZD drug. We used conditional logistic regression to estimate the crude and adjusted ORs for MNs, by subtype.

Results: We identified 820 cases (251 MDS, 472 CMPD, 92 AML, and five undefined MN cases) who met our inclusion criteria. There was a slightly increased risk of MN in users of BZDs compared with the referent group (adjusted OR 1.2, 95% CI 1.0, 1.4). The increased risk was present in the MDS and AML subtypes (adjusted ORs 1.6, 95% CI 1.1, 1.2; and 1.5, 95% CI 0.9, 2.7, respectively), but not in the CMPD subtype (adjusted OR 1.0, 95% CI 0.8, 1.3). The effect of BZDs was greater in the subgroup exposed only to long-acting BZDs than the subgroup exposed only to short-acting BZDs.

Conclusions: Exposure to BZDs may increase the risk of MDS and AML, but there is no evidence of an increased risk for CMPD. In this study we were able to evaluate use of BZDs for up to 20 years prior to the index date and to assess exposure in multiple ways, thereby addressing some of the limitations of earlier studies.

965. Abuse of Extended-Release (ER) and Immediate-Release Oxycodone in Kentucky Following Introduction of Reformulated ER Oxycodone

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Background: In August 2010, shipments of original extended-release (ER) oxycodone (OC) stopped and reformulated ER oxycodone (ORF) started. ORF is more difficult to crush and forms a gel when dissolved, but its effect on abuse is not known.

Objectives: To describe changes in rates of abuse, routes of administration (ROA), and frequency of abuse of ER oxycodone and immediate-release (IR) oxycodone following the introduction of ORF.

Methods: Structured interviews assessing opioid abuse, including past 30-day abuse, ROA, and frequency of abuse, were completed by 192 OC abusers in rural Kentucky. Participants reported retrospectively about their abuse in the pre-ORF period in July 2010, and concurrently about their abuse in the post-ORF period in interviews conducted December 2010–September 2011.

Results: Most respondents reported abusing OC in the month prior to the introduction of ORF (73%). Before ORF introduction, the prevalence of OC abuse in the sample was 25% for oral (average 0.3 days/month), 50% for snorting (11.6 days), and 51% for injecting (16.6 days). After ORF introduction, 59% reported abusing OC in past 30 days despite lack of availability through legal channels, and 33% reported abusing ORF. Abuse of ORF was mainly limited to oral ROA, with 21% reporting oral abuse (average 6.8 days/month), 5% snorting (4.2 days), and only one participant by injecting (1.0 day). Prevalence of IR oxycodone abuse increased from 74% to 96% pre- to post-ORF. Prevalence of non-oral abuse for IR oxycodone increased pre- to post-ORF from 57% to 70% for snorting and 45% to 51% for injecting; oral abuse remained stable at 30–32%. The frequency of IR oxycodone abuse increased for all ROA (oral: 4.1–12.3 days; snorting: 13.3–14.6 days; injecting: 12.6–20.3 days).

Conclusions: After its introduction, the prevalence of ORF abuse was lower than that of OC before ORF introduction, especially by non-oral ROA. ORF abuse remained constant over the post-ORF period as the availability of OC declined. A decline in OC abuse was accompanied by an increase in the prevalence and frequency of IR oxycodone abuse, particularly through non-oral ROA.

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966. Risk-Benefit Analysis of Therapy in Multiple Sclerosis

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Background: Benefit–risk (BR) analysis has been introduced by the European Medicines Agency to evaluate drugs as part of its approval process, but no systematic quantitative BR analysis is available for glatiramer acetate (GA) as a firstline therapy for relapsing-remitting multiple sclerosis.

Objectives: To undertake a systematic BR analysis of GA in relapse-remitting multiple sclerosis and clinical isolated syndrome using controlled studies, according to the EMA guideline.

Methods: We searched PubMed, Embase, the Cochrane Trials Register for eligible articles according to explicit criteria to obtain trials and controlled cohort studies. Fixed and random effects meta-analysis techniques were applied for pooling data. Qualitative and quantitative benefit-risk analyses were performed.

Results: A total of 4,451 patients in 15 studies were included in the meta-analysis. The overall reduction in clinical progression was 40% (RR = 0.60, 95% CI: 0.48–0.75) for GA compared with placebo/untreated and 23% (RR = 0.77, 95% CI: 0.65–0.92) for GA compared with interferons. The rate of patients free from relapse was higher with GA compared with placebo/standard treatment (RR = 1.35, 95% CI: 1.21–1.50) and similar compared with interferons (RR = 1.04, 95% CI: 0.98–1.11). For GA compared with interferons there was a13% reduction in discontinuation due to all causes (RR = 0.87, 95% CI: 0.72–1.04) and a similar proportion of serious adverse events leading to discontinuation (RR = 0.89, 95% CI: 0.56–1.41). Based on these results, for being free from disease progression at 24 months against placebo/untreated, the number needed to benefit was of 22.7 and the risk-benefit ratio was 1.69. Compared with placebo/untreated, the relative net benefit-risk was 9% using a multi-criteria decision analysis.

Conclusions: GA was found to reduce relapses and clinical progression compared with placebo, and clinical progression in comparison with interferons. Serious adverse events were comparable with interferons. Qualitative and quantitative methods demonstrated that the benefits of GA outweigh the risks but the results differ substantially depending on the quantitative risk-benefit model used.

967. Intensive Monitoring of Duloxetine, Results from a Web-Based Intensive Monitoring Study

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Background: Duloxetine (Cymbalta®) is a serotonin, 5-HT, and norepinephrine, NE, re-uptake inhibitor indicated for the treatment of depression, diabetic peripheral neuropathic pain and general anxiety disorder.

Objectives: The aim of this study is to gain insight in the user- and safety profile of duloxetine in daily practice, reported by patients via a web-based intensive monitoring system during their first 6 months of use.

Methods: First time users of duloxetine were identified through the first dispensation signal in the pharmacy. Patient demographics and information about drug use and ADRs were collected through electronic questionnaires sent 2 and 6 weeks, 3 and 6 months after start of duloxetine. ADRs were quantified and signal detection was performed on a case by case basis.

Results: Of 398 patients registered for the study. Of 69.1% were female. Depression was the main indication. Of 303 patients (76.1%) filled in at least one questionnaire and 78,9% of these reported an ADR. Serious ADRs were reported by four patients. Three new signals were identified, amenorrhoea, shock-like paraesthesias and micturition problems.

Conclusions: Web-based intensive monitoring is an observational prospective cohort study mirroring the use and ADRs of duloxetine in daily practice. This study indicates that duloxetine is a relatively safe drug as used by patients during 6 months in daily practice, but the aforementioned signals need to be evaluated in more detail. Web-based intensive monitoring shows to be a useful and efficient method to get insight in the behavior of new drugs in daily practice.

968. Nested Case–Control Study in Psychiatric In-Patients: AMSP +

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Background: From experiences with patients we learned that high plasma level and certain CYP450 genotypes are associated with a higher risk for SADR. However, there exist no studies in psychiatry which confirm this and might justify routine TDM and/or routine pharmacogenetic testing.

Objectives: Examine the feasibilty of a nested case–control study.

Methods: We performed a nested case–control study in the psychiatric in-patient hospital Königsfelden with 62 SADR cases and 82 matched controls in order to examine the feasibility of a nested matched control study design. In an open cohort, SADR according to the AMSP criteria were collected and analyses of the plasma concentrations of suspected drugs made. In this phase of the AMSP+ project, TDM but also pharmacogenetic tests were introduced to the clinicians. In a second phase 62 SADR cases were collected, drug plasma levels analysed, CYP2D6 genotyping and a midazolam test performed. These cases would be matched with three controls each, matching for the imputed drug (combination), gender and age group (<65 or ≥ 65 years old). Matching proved to be more difficult than expected and the original study design was changed to a non matched case–control study. The reasons were the heterogeneous patient population, drug combinations which were difficult to match and the difficult recruitment of controls.

Results: Preliminary results showed that the cases and controls were similar in age, gender, medication and also in weight, BMI, renal function and smoking behaviour. However, the odds ratio for drug plasma levels ≥120% of the upper reference limit was 3.49 CI95: 1.42–8.57 ($p = 0.005$) in SADR patients compared to the control patients. SADR patients had more often a CYP2D6 poor metaboliser genotype, controls more often a CYP2D6 ultra rapid genotype; however that was statistically no significant. Larger studies with more patients have to show if these results can be confirmed.

Conclusions: For future studies the difficulties of a nested matched control design has to be considered. A non-matched case–control study in a large cohort study seems more realistic and feasible. A multi-centre approach would help finding SADR cases and controls in a timelier manner.

969. Risk of Mortality (Including Sudden Cardiac Death) and Major Cardiovascular Events in Atypical and Typical Antipsychotic Users: A Study with the General Practice Research Database

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Background: Antipsychotics have been associated with increased mortality (including sudden cardiac death [SCD] and cardiac death) and major cardiac events.

Objectives: To assess mortality and other major cardiac events among antipsychotic users as compared to non-users.

Methods: The General Practice Research Database (GPRD) was used to identify cohorts of antipsychotic users, matched healthy controls and psychiatric diseased non-users. Outcomes (based on GPRD, Hospital Episode Statistics, death certificates and free-text search) included cardiac mortality, SCD (three separate definitions) overall mortality, coronary heart disease (CHD), and ventricular arrhythmias (VA). Sensitivity analyses were conducted for age, dose, duration, antipsychotic type, and psychiatric disease. Poisson regression was used to estimate relative rates (RRs) and 95% confidence intervals (CIs).

Results: Of 183,392 antipsychotic users (115,491 typical and 67,901 atypical), 544,726 healthy controls, and 193,920 psychiatric non-users were identified. Comparing antipsychotic users to psychiatric non-users the RR of mortality was 1.75 (1.64–1.87); for cardiac mortality 1.72 (1.42–2.07); for SCD primary definition 5.76 (2.90–11.45); for SCD secondary definition 2.15 (1.64–2.81); for CHD 1.21 (0.97–1.50); for VA 1.16 (1.02–1.31). Similar results were found when compared to healthy controls. RR of cardiac mortality was 1.74 (1.4–2.14) with atypicals and 1.88 (1.49–2.39) with typicals compared to psychiatric non-users. Incidences varied by age, dose, and duration. Non-users with schizophrenia, dementia, or bipolar disorder (assessed separately) had increased risks of mortality compared to healthy controls while non-users with major depression had comparable risks.

Conclusions: Cardiac and overall mortality was higher among antipsychotic users vs. controls. An increased risk of mortality was seen in non-antipsychotic users with schizophrenia, dementia or bipolar disorder. Limited SCD cases were available for evaluation.

970. Risk of Cardiac Mortality (Including Sudden Cardiac Death) in Olanzapine Users: A Study with the General Practice Research Database

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Background: Antipsychotics have been associated with increased mortality (including sudden cardiac death [SCD] and cardiac death) and major cardiac events.

Objectives: To assess the risk of cardiac mortality and other major cardiac events among patients treated with olanzapine and other antipsychotics compared to nonusers.

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Methods: The General Practice Research Database was used to identify cohorts of current antipsychotic users with psychiatric illness, psychiatric diseased nonusers, and matched healthy controls. Outcomes included cardiac mortality, SCD (three separate definitions), coronary heart disease (CHD), ventricular arrhythmias (VA), and overall mortality (excluding suicide). Sensitivity analyses were conducted for age, dose, duration, and psychiatric disease. Poisson regression was used to estimate relative rates (RRs) and 95% confidence intervals (CIs).

Results: Of 183,392 antipsychotic users (including 20,954 olanzapine users), 544,726 healthy controls, and 193,920 psychiatric nonusers were identified. There was no increased risk of all-cause mortality found in patients treated with olanzapine vs. psychiatric nonusers (adjusted relative risk [aRR]: 1.04, CI, 0.93–1.17), vs. an elevated all-cause mortality risk for all antipsychotic users (aRR: 1.75, CI, 1.64–1.87). There was a higher rate of cardiac mortality (aRR: 1.53, CI, 1.12–2.09) in patients treated with olanzapine vs. psychiatric nonusers, consistent with results for both atypical and typical antipsychotics. There was no increased risk of CHD or VA among patients treated with olanzapine vs. psychiatric nonusers, consistent with results for atypical antipsychotics and in contrast to patients treated with typical antipsychotics. Patients aged 30–64 had higher risks of all-cause mortality and cardiac mortality than those aged 65 and greater.

Conclusions: Patients treated with olanzapine were not found to be at increased risk of overall all-cause mortality vs. psychiatric nonusers. However, patients treated with atypical and typical antipsychotics, including olanzapine, had a higher risk of cardiac mortality vs. psychiatric nonusers. Limited SCD cases were available for evaluation.

971. Detection and Magnitude of Methylphenidate Abuse and Misuse Using Vigibase and Correlation with Level of Use in Europe

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Background: Methylphenidate (MPH) is a psycho-stimulant approved for the treatment of attention deficit and hyperactivity disorders. Recently, consistent data suggesting an increase of MPH abuse were identified in France with intravenous administration of crushed tablets. In the same way, a rise in MPH global availability has been identified in France and other European countries.

Objectives: To assess the relationship between the levels of consumption of MPH in European countries and MPH misuse or abuse reported to Vigibase, the WHO global ICSR database

Methods: Data were collected for all Continental European countries for the period 1994–2010. Data on MPH utilization were researched and extracted from national consumption statistics. Using Vigibase, individual case reports of MPH abuse, related with the WHO-ART terms "drug abuse" or "drug dependence" according to Caster's method (Caster 2011), were extracted. Trends in MPH abuse reporting were analysed using a bayesian confidence propagation neural network method, providing a statistical indicator, information component (IC) (Koren et al., 2011).

Results: Despite an extensive variability in the consumption levels, there is a common trend of growing MPH utilization in Europe, with a sharp increase since 2005 (+425% in Denmark (0.8–4.2 DID), + 67% in France (0.18–0.30 DID), +116% in Germany (1.0–2.16 DID) and +122% in Netherlands (2.04–4.53 DID) between 2005 and 2009). Preliminary results from VigiBase showed an increasing relative reporting rate over time for European reports with methylphenidate and drug abuse using the Information Component (IC), which is computed as the logarithm of a shrunk observed-to-expected ratio.

Conclusions: Analysis of the trends in MPH consumption, together with preliminary findings from Vigibase, is consistent with the existence of a positive relationship between the recent MPH increasing availability and the growing frequency of reported dependence-related ADRs. In a way to better understand and characterize this association, a quantitative in-depth analysis of these preliminary results will be undertaken.

972. Changes in Diversion Rates Following the Introduction of a Reformulated Extended Release Oxycodone Product

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Background: In August 2010, Purdue Pharma introduced reformulated extended release (ER) oxycodone (ORF) that is more difficult to crush and that forms a gel when dissolved and is intended to deter abuse.

Objectives: This study examines whether there was a decline in rates of diversion of ER oxycodone manufactured by Purdue following the introduction of ORF using data collected from drug diversion agents participating in the RADARS® System, an established surveillance system

for prescription drug abuse. Other prescription opioids were used as a comparator.

Methods: Diversion cases were obtained on a quarterly basis from law enforcement agencies. The Diversion Program surveyed 300 reporters in 50 states, covering 61% of the US population in the 3rd quarter of 2011. Diversion rates per 100,000 population and per 1,000 unique recipients of dispensed drug (URDD) were calculated for each quarter. October 1, 2008 through September 30, 2010 was considered the period before, and October 1, 2010 to September 30, 2011 the period after, introduction of ORF. The mean rate of drug diversion was compared before and after the introduction of ORF for ER oxycodone and other prescription opioids using negative binomial regression.

Results: There was a 47% decline (95% CI: 34–57%) in the ER oxycodone diversion population rate from 0.35 per 100,000 before to 0.18 per 100,000 after the introduction of ORF. There was a 45% decline (95% CI: 32–57%) in the ER oxycodone diversion URDD rate from 1.45 to 0.79 per 1,000 URDD before vs. after introduction of ORF. There was no significant change in diversion rates for other opioids.

Conclusions: These findings indicate that the introduction of the new formulation was followed by a decline in diversion of ER oxycodone manufactured by Purdue that did not occur for other prescription opioids. The decreased diversion of ER oxycodone to illegal channels suggests a decline in demand for the new formulation vs. the original formulation.

973. Risk Factors of Medication Non-Adherence in Depression and Anxiety, Preliminary Results

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Background: Depression has been shown a risk-factor for non-adherence to medication regimens. Non-adherence undermines optimal treatment of depression, anxiety and co-morbid conditions. Because non-adherence is difficult to identify in clinical practice, insight into risk factors of non-adherence is important to reveal non-adherence and optimise therapy.

Objectives: The aim of this study was to assess the rate of non-adherence, and risk factors for non-adherence in the Netherlands Study on Depression and Anxiety (NESDA), a large cohort study sample in a naturalistic setting.

Methods: All participants who used medication (n = 1899) at the 4 years follow-up of the NESDA cohort of 2,402 participants (age 22–69 years) were selected. The effects of patient-, disease-, and treatment-related factors on non-adherence, were analysed by means of univariate and multivariate regression. Adherence was assessed using the Medication Adherence Rating Scale (MARS).

Results: In univariate analysis, risk factors for non-adherence were lower age (OR = 1.16; $p < 0.001$), low social support (OR = 1.23; $p = 0.03$), higher IDS score (OR = 1.12; $p = 0.003$), higher neuroticism scores (OR = 1.11; $p = 0.023$), being employed (OR = 1.25; $p = 0.03$) and having a depression diagnosis (OR = 1.25; $p = 0.03$). In multivariate analysis, risk factors for non-adherence were lower age (OR = 1.19; $p < 0.001$), low social support (OR = 1.11; $p = 0.01$), higher IDS score (OR = 1.18; $p = 0.005$) and male gender (OR = 1.24; $p = 0.049$).

Conclusions: In this large study sample in a naturalistic setting, lower age, less social support, higher depression severity and male gender, are all risk factors for non-adherence. Clinicians should recognise these risk factors and apply adherence-improving strategies to improve patient outcome.

974. Antiepileptic Drugs and the Risk of Acute Hypothyroidism

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Background: Disturbance in thyroid function hemostasis associated with the use of antiepileptic drugs (AED) has been reported. However, AEDs related hypothyroidism remained controversial.

Objectives: To investigate the association between exposure of AEDs and hypothyroidism.

Methods: Electronic data sets containing 2 million individuals, which were randomly sampled from the National Health Insurance Research Database (NHIRD) in Taiwan, were used for this study. We selected thyroxine as an indicator of hyperthyroidism and performed a prescription sequence symmetry analysis (PSSA) from 2001 to 2009. The ratio of the patients initiating each AED after vs. before initiating thyroxine was described as the crude sequence ratio (SR). The adjusted SR and 95% confidence intervals (CI) were derived from dividing the crude SR by the null-effect SR. Two indicators, amiodarone and methimazole were selected to be internal and external standards respectively to test the sensitivity and specificity of PSSA. Besides, case–control (1:20) design were also conducted to test the robustness of the results of PSSA.

Results: In older AEDs, phenytoin (adjusted SR, 1.92; 1.55–2.39), carbamazepine (1.20; 1.01–1.46) and valproate

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(1.44; 1.15–1.80) associated with higher risk of acute hypothyroidism. On the contrary, newer generation AED had irrelevant association of hypothyroidism, such as clonazepam (1.09; 0.91–1.18), gabapentin (0.95; 0.70–1.3), oxcarbazepine (1.42; 0.88–2.31). Significant associations were found in the pairs of amiodarone and thyroxine (adjusted SR, 2.23; 95% CI, 1.82–2.72), and irrelevant association was found in the pairs of each AED and methimazole. The results in case–control design showed similar trends to PSSA that greater hypothyroidism risk toward to older AEDs.

Conclusions: Our findings indicated that acute hypothyroidism was associated with older generation AED. Patients were suggested to be closely monitored thyroid function when receiving the regimen. Besides, this study would also support the good applicability of PSSA method under Taiwan national health system.

975. Emergency Department Visits and Inpatient Admissions for Opioid Abuse-Related Events: National Estimates for the United States (2006–2008)

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Background: The epidemiological burden of the nonmedical use of opioid analgesics in the United States (US) is not completely understood, especially with regards to health services utilization and payer type.

Objectives: To determine national estimates for emergency department (ED) visits and inpatient admissions for patients with opioid abuse-related diagnoses, categorized by insurance status.

Methods: We used the 2006, 2007, and 2008 files of the US-based Healthcare Cost and Utilization Project's Nationwide Emergency Departments Sample (HCUP-NEDS) to identify events assigned opioid abuse, dependence, or poisoning ICD-9-CM diagnosis codes (304.0X, 304.7X, 305.5X, 965.00, 965.02, 965.09). Estimates were computed using the "svy" commands in Stata SE 9.0 (StataCorp, College Station, TX, USA) to account for the complex sampling design of the data set.

Results: The number of opioid abuse-related ED visits increased 9.4% over the study period (515,896; 506,837; and 564,559 for 2006, 2007, and 2008, respectively). Of these, Medicaid was the expected primary payer for approximately 30% of ED events in all 3 years, followed by self for 25% events, private insurance for 20% events, and Medicare for 17%. The number and proportion of events for which the patient was admitted as an inpatient to the same hospital from the ED was 274,848 (53.28%); 281,385 (55.52%); and 303,468 (53.75%) for 2006, 2007, and 2008, respectively. Medicaid was the expected primary payer for approximately 34% of events resulting in inpatient admission (in all 3 years), followed by Medicare for 21%, and private insurance for 20% events. Self-payment for opioid abuse-related inpatient admissions showed some variation in proportion from 21.85% in 2006 to 16.54% in 2008.

Conclusions: We found an increase in the number of opioid abuse-related events from 2006 to 2008. Approximately 50% of events were paid for by government-funded plans. An understanding of the true burden of opioid misuse, epidemiologic as well as economic, is essential to guide prescription monitoring programs, risk management strategies, as well as policy.

976. Cannabis Disorders Reported to the French Monitoring System of Abuse and Dependence: Increasing Reporting of Serious Cardiovascular Disorders

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Background: Cannabis is known to be associated with neuropsychiatric troubles, and less to complications affecting other specified body systems. Several outstanding cardiovascular complications following cannabis use were reported to the French Network of Addictovigilance Centres (CEIP-A) during the recent years.

Objectives: This study aimed to summarize and evaluate the cardiovascular complications of cannabis reported to the French monitoring system of abuse and dependence.

Methods: We identified all spontaneous reports (NotS) of cardiovascular complications related to cannabis use collected from 2006 to 2010 by the 13 French CEIP-A. Clinical characteristics of these cases and their evolutions were described.

Results: Among all NotS involving cannabis exposure, 2% were cardiovascular complications. Patients were mainly males (85.7%) with a mean age of 34.3 years old (SD 8.8). Cases were characterised by three cerebral, 10 peripheral and 22 cardiac complications including 20 cases of acute coronary syndromes. "Acute cerebral angiopathy", "transient cortical blindness" and "spasm of cerebral artery" were reported as cerebral complications. Peripheral complications consisted in arteriopathies such as Buerger-like diseases. The follow-up of these reports identified nine deaths in patients with cardiac complications whereas 19 patients were hospitalised for acute coro-

nary syndrome. Management of hospitalised patients comprised non-invasive and invasive techniques (i.e., cardiac repermeabilisation, limb amputation).

Conclusions: Cannabis derivatives were shown to lead to cardiovascular complications through mechanisms involving the autonomous nervous system. These complications represent about 2% of all adverse events related to cannabis use reported to the French system of drug abuse monitoring. Even though these complications are more likely observed among young adults who use stimulant drugs, practitioners should be aware that cannabis may work as other illicit psychoactive drug (cocaine or amphetamine) and may be a potential triggering factor for cardiovascular complications in young people.

977. The Association between Class and Dose Level of Antidepressant Medication with Suicidal Behaviors

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Background: Antidepressant (AD) medications are among the most prescribed in the US, yet given the FDA black-box warning that AD use may increase risk for suicidal behaviors, it is of critical importance to further understand the safety of these medications. However, the research examining the association between AD class and risk for suicidal behaviors has mixed results, and no research to date has assessed whether AD dose level is associated with suicidal behaviors.

Objectives: To determine whether the rate of non-fatal suicide attempts is differential by AD class, and whether the rate is differential by dose among the largest class of selective serotonin reuptake inhibitor (SSRI) users.

Methods: A new-user cohort study design was implemented in a healthcare utilization dataset that further includes prescription drug use and medical and psychiatric conditions, 1998–2010. Subjects identified with depression that were new users of any class of AD (SSRI; serotonin-norepinephrine reuptake inhibitor [SNRI]; tricyclic [TCA]) were followed prospectively. Suicidal behaviors were assessed via medical records. Propensity-score matching was used to adjust for confounding, with analyses comparing SNRI to SSRI users (N = 279,693; mean follow-up 218 days), TCA to SSRI users (N = 89,570; mean follow-up 200 days), and high to low dose among SSRI users (N = 159,513; mean follow-up 216 days).

Results: No significant difference in the rate of suicide attempts was observed when comparing SNRI to SSRI users (hazard ratio [HR]: 1.17; 95% CI: 0.96–1.42). The rate of suicide attempts appeared slightly, but not significantly, lower for TCA compared to SSRI users (HR: 0.68; 95% CI: 0.43–1.09). Among SSRI users, there was no significant difference when comparing high vs. low dose (HR: 0.88; 95% CI: 0.73–1.07).

Conclusions: Pending age-stratified analyses, it does not appear that class or dose of AD should influence concerns of suicidal behavior among depressed patients on AD. Prescribing preferences could be based on other clinical considerations.

978. Prevalence of Migraine in United States (U.S.) Emergency Departments (EDs) and the Association between Weekend ED Admissions and Opiate Use

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Background: Migraine is a common reason for emergency department (ED) visits in the U.S. Although other treatment options exist, opioids are commonly prescribed as rescue therapy in this setting.

Objectives: The purpose of this study was to determine the prevalence of migraine in U.S. EDs, describe opioid utilization, and explore potential factors contributing to the utilization of opioids in this setting.

Methods: Patients aged 18+ with a migraine diagnosis (ICD-9 = 346.xx) in a U.S. ED setting were identified from the Cerner Health Facts® electronic medical records database between January 1, 2000 and December 31, 2010. Weekend admissions occurred between Friday and Sunday evenings. Opioids administered on the same day of the ED admission were examined. Multivariate logistic regression was performed to examine the association between weekend admissions and opioid use after controlling for demographics, concomitant cardiovascular, pain and psychiatric diagnoses.

Results: Among 4.7 million ED visits, the prevalence of migraine was 1.2% (annual range = 1.0%–1.5%). Compared with non-migraine patients, migraine patients were significantly younger (mean age in years: 38 vs. 44) and female (85% vs. 58%). The utilization of opioids among migraineurs was 47%. After adjusting for age, gender and concomitant diagnoses, migraineurs admitted to the ED on weekends were significantly more likely to receive opioids than those admitted on weekdays (odds ratio = 1.14, CI = 1.10 to 1.18, p-value < 0.0001).

Conclusions: Consistent with previous studies, migraine is an important reason for ED visits and opiates are frequently used as rescue therapy despite the U.S. headache consortium recommendation to use non-opioid treatments for migraine in the ED. A significant predictor of opioid administration was a weekend visit. Reasons for the increased likelihood of receiving opioids during weekends need to be studied. It may be that demographics and clinical features of those seeking care vary in weekends relative to weekdays. Alternatively, physicians attitudes toward

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migraine treatment may also be influenced by working on weekends.

979. Predictors of Severe Pain in a Cohort of 9,185 Individuals with Self-Reported Neuropathic Pain

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Background: The influence of pain descriptors and mechanical hypersensitivity on pain severity in neuropathic pain is not well understood.

Objectives: To analyze the factors predicting severe pain in a large cohort of subjects self reporting neuropathic pain.

Methods: Patients with chronic pain from a large database were contacted. A pain questionnaire was given to 9,185 who were potential subjects aged 18–80 years for a Phase IIa clinical study and questionnaire data was analyzed. This study focused on mechanical hypersensitivity, pain descriptors and duration of pain. Multiple logistic regression models were used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CI) for pain severity and other factors associated with neuropathic pain (NP).

Results: Mean age was 50.0 years (SD = 12.9) and 63.5% were women. The odds ratio for severe pain (NRS 7–10) compared to mild pain (NRS 1–3) was 1.4 (95% CI 1.1–1.8) for women. Older (60–80 years) and middle aged (40–59 years) subjects had a slight but significant increased odds ratios for severe pain (1.4/1.5 respectively) compared to younger subjects (18–39 years). In reference to mechanical hypersensitivity (MH), patients reporting allodynia had an odds ratio for severe pain of 2.7 (95% CI 2.0–3.6) and patients reporting hyperalgesia had an odds ratio of (4.8 [95% CI 3.6–6.4]). Those self reporting both allodynia and hyperalgesia had an odds ratio for severe pain of 12.7 (95% CI 9.3–17.4) compared to those with neither condition. Five pain descriptors (burning, shooting, aching, shocking, and other) were identified. Those reporting three or more pain descriptors had an odds ratio of 6.0 (95% CI 2.6–13.7) compared to those without descriptors. The presence of a mental disorder had an odds ratio for severe pain of 1.5 (95% CI 1.1–1.9). The odds ratio tended to increase with duration of pain.

Conclusions: Gender, age, and mental disorders were similarly predictive of severe pain. MH was strongly indicative for severe pain with a significant interaction of both factors in severe pain. An increasing number of pain descriptors was also strongly predictive of severe pain.

980. Descriptive Characteristics of 12,771 Potential Subjects for a Phase IIa Clinical Study in Neuropathic Pain

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Background: There is sparse population based information on the epidemiology of chronic neuropathic pain.

Objectives: To characterize a large population of potential subjects for a Phase IIa clinical neuropathic pain study.

Methods: In total, 12,771 subjects 18–80 years of age responded to a questionnaire asking information about pain and neuropathic symptoms. The mean and standard deviations for continuous variables and frequencies for categorical variables were calculated. The restrictive nature of the planned phase IIa study will to some extent lead to selection bias and generalization/interpretation of the results to a broad neuropathic pain population must proceed cautiously.

Results: Of the 12,771 reporting chronic pain, 9,185 self reported neuropathic pain (NP), of those 78.9% were not eligible for the study based on questionnaire data. Main causes of disqualification in descending order were: (1) pain duration > 5 years; (2) specific pain diagnosis; and (3) a history of a mental disorder. Among those who reported neuropathic pain, the mean age was 50.0 (SD = 12.9) years. The major causes of NP chosen by subjects from the questionnaire were: (1) post traumatic neuralgia (40.5%); (2) lumbosacral radiculopathy (30.4%); and (3) non-diabetic polyneuropathy (16.5%). Frequency of reported pain descriptors was similar for burning (14.0%), shooting (13.9%) and aching (15.4%), but less frequent for shocking (9.5%). Self reported mechanical hypersensitivity symptom frequency was 77.0% for "pain from light touch", and 77.4% for "increased response to a painful stimulus". About one half reported their pain as severe (NRS 7–10). Two thirds of subjects had pain duration of more than 1 year, one third more than 5 years.

Conclusions: We report descriptive characteristics of a large cohort of potential subjects with neuropathic pain volunteering for a clinical study. The restrictive nature of phase IIa studies may result in a small fraction of patients being appropriate for inclusion. Such low eligibility may contribute to recruitment difficulties and potential selection bias. Extrapolation of results from such studies to a general population must be considered with caution.

981. Risk of Developing Alzheimer's Disease in Association with Influenza Infections

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Background: Several epidemiological studies suggest a potential involvement of viral pathogens in the development of Alzheimer's disease (AD). While recent research focuses on herpes simplex virus type 1 (HSV-1), the role of influenza infection or vaccination is largely unknown.

Objectives: To explore the association between influenza infection, exposure to influenza vaccines and the risk of developing AD in a large population-based study.

Methods: We conducted a case–control analysis using the UK-based General Practice Research Database (GPRD). We identified cases aged 65 years or more with an incident diagnosis of AD between 1998 and 2008, and we matched one control patient without dementia to each case on age, sex, general practice, calendar time, and years of history in the database. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of developing AD in relation to previous influenza infections, to a subgroup of influenza infections that occurred within 1 year after an influenza vaccination, or to another subgroup of influenza infections that were followed by bacterial superinfection (indicated by an antibiotic treatment within 30 days), stratified by number of infections and adjusted for various potential confounders.

Results: We identified 7,086 cases with an incident diagnosis of AD and the same number of matched controls. After adjusting for various potential confounders, a history of influenza infection was not associated with an altered risk of developing AD; the OR for patients with three or more previous infections was 0.96 (95% CI 0.49–1.88). In the subgroups of those who developed an influenza infection despite a previous influenza vaccination or those who received antibiotic treatment, the OR of developing AD was not altered either.

Conclusions: In the current study population, a history of influenza infection was not associated with an altered risk of developing AD.

982. The Prevalence of Diagnosed Depression and Depression Risk Factors in US Managed Care HIV Patients Compared to the General Population without HIV

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Background: Depression is common in HIV patients, though prevalence estimates vary. The purpose of this study was to update the epidemiology of depression in the HIV population.

Objectives: The objective was to determine the annual and period prevalence of diagnosed depression, stratified by age and sex, in HIV patients compared to the general population without HIV.

Methods: Patients ≥18 years old were identified from the Thompson-Reuters MarketScan Commercial Claims and Encounters Database (Q1/2004-Q3/2010). This database represents employed patients in the United States (US) with managed health care. Patients with ≥2 HIV diagnoses (ICD9-CM 042) were classified as HIV-positive. Patients without any diagnosis of HIV were classified as the HIV-negative population. Annual and period prevalence of any diagnosis of depression (ICD9-CM 311.xx, 296.2x, 296.3x, 300.4) was calculated for each group and compared using prevalence ratios between the two groups. Stratifications by sex and age were also compared.

Results: Of 234,668 HIV-positive patients and 130,699,609 HIV-negative patients met inclusion criteria. The period prevalence of diagnosed depression was 1.48 times higher in HIV-positive patients compared to the HIV-negative population (3.68% [n = 8635] vs. 2.48% [n = 3,243,433], respectively). Annual prevalence ratio estimates ranged from 1.40–1.55. Within the HIV-positive population, female (3.88%) and male (3.62%) prevalence of diagnosed depression were similar. Comparing the HIV-positive to the HIV-negative population, the prevalence ratio of depression in females (1.28) was lower than that for the male-only population (2.00) though both estimates showed increased prevalence of depression in the HIV-positive population.

Conclusions: An HIV diagnosis is associated with diagnosed depression in US managed care. Unlike the general population where female sex is a substantial risk factor for depression, risk for depression in patients with a HIV diagnosis is similarly high for both sexes. These results suggest the importance of increased screening for depression in the HIV population regardless of sex.

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983. Use of Second Generation Antipsychotic Drugs during 1990 to 2009

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Background: The evaluation of antipsychotic medication use patterns during long periods provide, substantial information about the antipsychotic drugs most frequently prescribed.

Objectives: The present study was aimed to evaluate the evolution of antipsychotic drugs use in outpatients during 1990–2009 (ATC classification N05A group) in Extremadura (Spain).

Methods: Data over a 20-year period (1990–2009) regarding antipsychotic medication prescribing was drawn from all community pharmacy figures on drug expenditures derived from the Extremadura Healthcare reimbursement system. Drug consumption figures were expressed as the number of defined daily doses per 1,000 inhabitants and per day of treatment (DDD/1,000/day).

Results: Antipsychotic drugs utilization increased from 1.98 (1990) to 8.65 DDD/1,000/day (2009) in Extremadura. Of the total antipsychotic consumption, haloperidol (30%) and olanzapine (29%) were the most frequently prescribed in Extremadura during 1990 and 2000, respectively. The use of second-generation antipsychotic drugs (SGAs) increased from 0% in 1990 to 1993 to 86% in 2009. Olanzapine was the most used SGA from 1999 to 2009.

Conclusions: The use of antipsychotic drugs has increased over the last years. Since SGAs became available in the mid-1990s, they appear to have largely replaced typical or first-generation antipsychotics as the treatment of choice for chronic mental disorders such as schizophrenia.

984. Clinical Study on Psychotropic Drug Induced Weight Gain and Other Metabolic Complications in a Swiss Psychiatric Population

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Background: Despite a better overall tolerance compared to classical antipsychotics, atypical antipsychotics (AP) are strongly related to side effects, such as metabolic disorders.

Objectives: To analyze the weight gain-related side-effects of psychotropic drugs and their consequences on metabolic complications in a large Swiss cohort of psychiatric patients (n = 561).

Methods: A cross-sectional observational study (n = 188) was performed in an out-patient psychiatric division with patients having received for more than 12 months the following drugs: clozapine, olanzapine, quetiapine, risperidone, lithium, amisulpride, aripiprazole and/or valproate. Another longitudinal study consisted of a follow up of patients being prescribed the same drugs for up to 1 year (n = 373). Prevalence of BMI and weight gain was calculated for each group.

Results: For the cross-sectional study, the mean age was 41 years (range: 18–69). Weight gain (≥10% of initial weight) following drug treatment was reported in 43% of these patients. A high prevalence of overweight (BMI: 25–30) or obesity (BMI > 30) was found in this cohort (63%). For the longitudinal study, the mean age was 48 years (range: 12–96). An increase in the overweight or obesity prevalence was found during treatment in adults (33%, 35%, 46% and 57%, before, after one, 3 and 12 months of treatment, respectively) and in children (21%, 29%, 31% and 50%, respectively).

Conclusions: High prevalence of overweight or obesity was found in an outpatient psychiatric population and confirms drug-induced weight gain complications during long-term treatment. Results on other clinical factors of the metabolic syndrome as well as on analyses of genetic factors linked to obesity and metabolic syndrome will also be shown. This study supports the recently published recommendations to monitor metabolic side effects during treatment with atypical antipsychotics and/or mood stabilizers. This could help to identify patients with special health care management requirements.

985. Abstract withdrawn by author.

986. Characteristics Associated with Delays in Diagnosis of Pompe Disease among Patients Enrolled in the Pompe Registry

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Background: The rarity and variable presentation and progression of Pompe disease cause a low index of suspicion for the disease, often resulting in delays in diagnosis. The Pompe Registry tracks the disease and treatment outcomes of patients.

Objectives: Describe the diagnostic gap (time from onset of Pompe-related signs/symptoms to Pompe diagnosis) in the Registry and identify clinical and demographic characteristics related to this gap.

Methods: We conducted a cohort analysis stratified by Pompe-related symptom onset category (defined by age at Pompe-related symptom onset and the presence of cardiomyopathy). The median diagnostic gap was calculated for each onset category and according to demographic and clinical characteristics. Outliers (patients with a diagnosis gap >90% of the median) were reviewed and assessed for data validity and consistency. Multivariate logistic regression analyses were performed for each onset category to identify factors that predict the outcome of a diagnostic gap greater than the median gap for the onset category. Sensitivity analyses were conducted by shifting the variable definitions and assumptions.

Results: As of October 2011, 647 patients in the Registry were eligible for the study population. Patients were classified into three onset categories: Group A (N = 103): symptom onset ≤1 year of age with cardiomyopathy; Group B (N = 118): onset ≤1 year without cardiomyopathy and onset >1 year to ≤12 years; Group C (N = 426): onset >12 years. Group B had the largest diagnostic gap (12.6 years), followed by Group C (6.0 years) and Group A (1.4 months). Presenting sign/symptom class was the only significant independent predictor of a long diagnostic gap in Group A ($p = 0.01$). In Groups B and C, age at symptom onset ($p < 0.0001$ and $p = 0.0003$), year of diagnosis ($p = 0.02$ and $p = 0.02$), and first sign/symptom class ($p = 0.005$ and $p < 0.0001$) were all significant.

Conclusions: Despite available, reliable diagnostic methods, significant diagnostic gaps across the disease spectrum in Pompe patients continue. Presenting signs/symptoms (all onset categories) and age at symptom onset and year of diagnosis (older onset categories) predict a long diagnostic gap.

987. Methods of Diagnosis of Patients with Pompe Disease: Data from the Pompe Registry

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Background: Pompe disease is diagnosed by revealing reduced or absent acid α-glucosidase activity in blood-based assays (such as lymphocytes or dried blood spots), fibroblasts from skin biopsies, or muscle biopsies. The Pompe Registry tracks the disease and treatment outcomes of patients.

Objectives: Determine diagnostic methods used in the Pompe Registry and assess if they varied by demographic and clinical characteristics and how methods changed over time.

Methods: A cross-sectional analysis was conducted on all patients enrolled in the Registry with a reported method of diagnosis. Methods reported were categorized as DNA, enzyme, and other testing. "Other" includes all write-in responses that could not be recoded to DNA or enzyme analysis and was further categorized into muscle biopsy and other. Enzyme was categorized by type of assay. Patients could report more than one type of method of diagnosis and type of enzyme assay. Percentages of patients with a reported method of diagnosis were calculated according to demographics and clinical characteristics of Pompe disease.

Results: Diagnosis data were available for 891 of 908 enrolled Registry patients (as of September 2010). Enzyme assays alone were used in 37% of patients. Combined use of both DNA and enzyme diagnostic assays showed an upward trend over time: 17% (pre-2000) to 41% (2008–2009). Patients with symptom onset ≤1 year of age with cardiomyopathy were more likely to report receiving any enzyme analysis and less likely to report receiving a muscle biopsy than other patients. Patients who presented with respiratory symptoms were less likely to report receiving muscle biopsies than patients with other presenting symptoms. Among patients diagnosed with enzyme-based methods, blood-based assays were most common and increased over time. Multiple diagnostic methods were used in approximately half of all patients.

Conclusions: Among Pompe Registry patients, blood-based assays have become the most commonly used diagnostic method. Increased use of these assays for screening for Pompe disease may lead to earlier diagnosis and timelier treatment. Use of more than one method is helpful in confirming a diagnosis and identifying patients sooner.

988. Comparison of the Use of Endocrine Therapy for Women with Breast Cancer in Australia and Several European Countries

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Background: Endocrine therapies, aromatase inhibitors and tamoxifen, are commonly used as an adjuvant treatment in women with breast cancer.

Objectives: To compare the patterns of use of endocrine therapies for breast cancer between Australia and several European countries, and investigate possible factors contributing to these patterns.

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Methods: The endocrine therapies studied were tamoxifen and the Aromatase Inhibitors (AIs) anastrozole, letrozole and exemestane. Drug utilisation data were collected from nine countries: Australia, Denmark, England, Finland, France, Iceland, the Netherlands, Norway and Sweden, and converted to DDD/1,000 inhabitants/day to enable comparison. Data were further adjusted for female population and breast cancer incidence in each country, to be expressed as DDD/1,000 new breast cancer cases/day.

Results: Usage of total endocrine therapies either increased or remained steady in all countries between 2001 and 2009. After adjustment for breast cancer incidence, England showed the highest overall usage, twofold greater than the Netherlands with the lowest usage. Tamoxifen usage showed a downward trend across all countries, in conjunction with an increased uptake of the AIs. By 2008 the AIs represented over 50% of total endocrine therapy usage in all countries except France, where AI usage was 75% of the total due to a more rapid AI uptake. Compared with the European countries, Australia showed a relatively slow AI uptake and a lower use of endocrine therapies overall.

Conclusions: The similar general trends across all countries may be due to relatively comparable healthcare systems, particularly in terms of pharmaceutical coverage. Some of the usage differences may be due to variations in prescribing patterns and reimbursement timing.

989. Development of a Distributed Research Network in Japan: A Pilot Study on Antiemetics Use for Chemotherapy-Induced Nausea and Vomiting

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Background: Most of the large hospitals in Japan own computerized ordering and billing systems but little is explored in their usefulness as a secondary data analyses tool.

Objectives: The objective is to describe our experiences on developing and implementing a distributed research network of hospital data for a nationwide, cross-sectional antiemetic utilization survey.

Methods: Thirty-five large hospitals with in-/out-patients' detailed daily treatment records were participated: four owned a standardized ordering data repository system with the rest provided their billing data via Medical Data Vision Co., Ltd. Data for patients under injectable chemotherapies was extracted locally and standardized into a minimum dataset by distributing R Codes. Datasets were collected with execution logs monitoring any unexpected errors and integrated for analyses.

Results: Records of 75,222 chemotherapy cycles for 9,367 patients between 2010/1/1 and 2011/6/29 were obtained within 2 months from the first setup meeting and without a financial sponsor. By extracting and processing the data, we experienced e.g., missing data, discordance of drug name and code, and partial but systemic paper-based ordering. Some sites allowed a comma for data entry which affected data output in CSV (comma-separated values) format. All the issues were manageable and valuable to improve the system for secondary data use.

Conclusions: The network was workable even without an expensive statistical software and data handling skills. Master agreement and central Ethics Review Committee would shorten the study timeline > 30 days. With a strong local control of data, only minimal required data was centralized, assuring data holders' participation. This network, however, is applicable for selected research questions: linking with other data sources will enable to explore wider variety of clinical researches.

990. Use of Cetuximab (CTX) in 1st-Line Therapy of Metastatic Colorectal Cancer (mCRC): Patient Characteristics, Safety and Effectiveness in the EREBUS Cohort

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Background: CTX has demonstrated improved survival outcomes in mCRC but information in real-life is sparse.

Objectives: Presented here are patient characteristics, safety and effectiveness for those included in 2009.

Methods: EREBUS is a French multicentre (n = 92) cohort. Patients (pts) initiating CTX 1st-line therapy for unresectable mCRC in 2009–2010 were identified from dispensation registries and followed 12 months.

Results: A total of 205 pts were included, all had wild-type (wt) KRAS gene. Median age: 64 years, 67.3% male, 65.8% ECOG = 0–1, 61% cardiovascular history, 78.5% colon primary site, 73.7% synchronous metastasis, single metastatic site: 52.7% (39% exclusively liver). A multidisciplinary team considered 1st-line as palliative for 61.5% of pts, and 37.1% as potentially resectable. CTX was com-

bined with oxaliplatin-based regimens: 37.6%, irinotecan-based regimens: 55.6%, and other regimens: 6.8%. For those receiving CTX + oxaliplatin (n = 77): median duration of CTX use was 3.6 months and 63.6% were treated every 2 weeks. For those receiving CTX + irinotecan (n = 114): it was 4.7 months and 81.6% treated every 2 weeks. Response rate according to physician evaluation was 48.6% for CTX + oxaliplatin and 46.8% for CTX + irinotecan. One-year OS was 59.9% (95% CI 47.6–70.2) and median PFS was 8.6 months (6.3–10.5) for CTX + oxaliplatin. One-year OS was 69.1% (59.6–76.7) and median PFS was 9.3 months (7.4–10.5) for CTX + irinotecan. Incidence of any grade 3/4 event was 58% for CTX + oxaliplatin and 57% for CTX + irinotecan: neutropenia (18.2% and 19.3%, respectively), skin reaction (11.7% and 14%), asthenia (11.7% and 14.9%), hypokalaemia (13% and 4.4%), diarrhoea (6.5% and 10.5%) and infusion-related reactions (1.3% and 0.9%). Surgical evaluation was performed in 27.8%: 31.2% CTX + oxaliplatin and 24.6% CTX + irinotecan.

Conclusions: In France, CTX was frequently combined with irinotecan-based regimens in 1st-line wt KRAS mCRC. These results indicate a high proportion of exclusive liver metastases, and a high proportion of patients undergoing surgery. Effectiveness and safety profile of CTX in real-life were in line with pivotal trials.

991. The Impact of Depression on Interferon-Containing Therapy Initiation and Discontinuation among HCV Patients in a US Managed Care Population

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Background: Interferon alpha is a component of currently available HCV treatment regimens. However, interferon is associated with substantial contraindications and adverse events, including depression, which can potentially affect a patient's ability to initiate and remain on therapy. Indeed, depression has been associated with a decreased probability of adherence in multiple therapeutic areas[1].

Objectives: The prevalence of depression was examined, as well as its impact on interferon-containing therapy (ICT) initiation and discontinuation, among HCV patients in a managed care setting.

Methods: Claims data from the MedStat MarketScan database (years 2005–2010) were used to identify incident HCV patients who had ≥2 years of continuous enrollment (≥1 year before and after first diagnosis). The impact of a history of depression (based on ICD-9 codes) in the year prior to first observed HCV diagnosis on ICT initiation was assessed, as well as its impact on time to discontinuation. Significance was accepted at 5%.

Results: Of 15,409 incident HCV patients were identified between 2005 and 2010, 3,282 (21%) of whom received ICT after HCV diagnosis. Depression was present in the year prior to first observed HCV diagnosis among 262 (8.0%) and 1,117 (9.3%) of patients who did and did not receive ICT, respectively. A recent history of depression was significantly associated with a lower probability of receiving ICT after HCV diagnosis (p = 0.02). However, there were no differences in time to ICT initiation among individuals with and without depression. Patients who had depression diagnoses prior to initiating ICT had shorter times to discontinuation than patients who did not (mean time to discontinuation = 5.7 months and 6.2 months, respectively, [p = 0.01]).

Conclusions: In this study of new HCV patients, a recent history of depression was found to be a barrier to initiating ICT. For patients who received ICT, those with a recent history of depression had no difference in time to ICT initiation but had a shorter time to ICT discontinuation than those without a recent history of depression.

Reference 1 DiMatteo M, et al. *Arch Intern Med* 2000;160:2101–07.

992. Use of Hospital Discharge Data To Monitor Trends in Chemotherapy Use among Individuals Diagnosed with Stage III Colon Cancer in Denmark, 2004–2009

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Background: Over the past 10 years, randomized controlled trials of new chemotherapeutic regimens for stage III colon cancer have demonstrated significant survival benefits. However, dissemination of this evidence into clinical practice in Denmark is largely unknown.

Objectives: To estimate the prevalence of chemotherapy utilization and to assess trends in use of specific regimens from 2004 to 2009.

Methods: We drew upon population-based registries and medical databases to conduct a cross-sectional study of chemotherapy utilization in Denmark Individuals diagnosed with primary stage III colon cancer from 2004 to 2009 were identified from the Danish Cancer Registry. Chemotherapy regimens were defined using treatment codes obtained from the Danish National Registry of Patients for 3 months following diagnosis. For all individuals receiving chemotherapy in hospitals that reported >80% of chemotherapy claims with specific codes, we determined the number and proportion treated with prespecified regimens and estimated trends in annual prevalence using logistic regression.

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Results: Overall, 1,984 individuals (57%) received adjuvant chemotherapy treatment within 3 months of diagnosis, with steadily increasing rates over time ($p < 0.001$). Among those treated with chemotherapy in hospitals reporting specific codes (n = 908), treatment with 5-fluorauracil (5-FU) was the most common regimen in 2004, accounting for 46% of all chemotherapy administered. However, its use as a single agent declined over time. Capecitabine, an oral form of 5-FU, replaced a large portion of 5-FU use, with a prevalence of 14% in 2008. From 2005 on, utilization of oxaliplatin + 5-FU (FOLFOX) quickly increased, peaking at 38% in 2007. Oxaliplatin + capecitabine (XELOX) then overtook FOLFOX as the most common regimen, accounting for 56% in 2009.

Conclusions: For single agent regimens, use of 5-FU decreased over time, partially due to increased capecitabine use. The uptake of combination regimens was rapid during the study period, starting with increased use of FOLFOX and followed by a shift to XELOX. This suggests rapid dissemination of trial evidence into clinical practice.

993. Patterns of 6-Mercaptopurine and Azathioprine Maintenance Therapy among Commercially Insured Individuals Diagnosed with Crohn's Disease in the US

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Background: Thiopurines (6-mercaptopurine [6-MP] and azathioprine [AZA]) are the mainstay of maintenance therapy for Crohn's disease (CD). However, studies examining their effectiveness in routine clinical practice are lacking.

Objectives: To describe the effectiveness of 6MP/AZA maintenance treatment and patterns of subsequent therapy among a cohort of commercially insured individuals diagnosed with CD and initiating 6-MP/AZA monotherapy between 2001 and 2008 in the US.

Methods: Using the Thomson Reuters MarketScan databases, which included healthcare utilization and enrollment data for > 24 million enrollees in the US in 2008, we identified all individuals diagnosed with CD and initiating 6-MP/AZA from 2001 to 2008 (n = 3,657). We estimated the proportion of CD patients remaining on 6MP/AZA monotherapy using nonparametric Kaplan-Meier survival analysis and identified predictors of treatment non-continuation using multivariable Cox proportional hazards models. The number and proportion of clinical events preceding treatment non-continuation and changes to maintenance therapy after non-continuation were reported.

Results: The overall one-year continuation rate of 6-MP/AZA treatment was 42%. Children (age < 18) and individuals with no prior use of anti-TNFs were more likely to continue 6MP/AZA treatment, while those dispensed more outpatient prescriptions for any drug prior to 6MP/AZA initiation (> 4) were less likely to continue maintenance treatment. Overall, 1,128 (40%) and 105 individuals (4%) of individuals experienced a clinical event potentially indicative of active disease or 6MP/AZA intolerance prior to non-continuation, respectively. Excluding full discontinuation of CD treatment, most individuals who failed to continue on 6MP/AZA augmented their treatment with an anti-TNF.

Conclusions: Most patients initiating on 6MP/AZA treatment did not continue beyond 1 year. In contrast to RCT evidence showing one-year remission rates of 40–90%, the lower effectiveness of 6MP/AZA treatment shown in this study may be due to differences in a variety of factors such as patient demographics, comorbidity, monitoring, and healthcare utilization.

994. Adherence with Oral Anticancer Agents

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Background: In the past decade the availability and use of oral anticancer agents have increased substantially.

Objectives: To determine the adherence and its determinants in patients using an oral anticancer agent.

Methods: In this observational multicenter study patients were extracted from pharmacy databases of outpatient pharmacies of four Dutch academic hospitals. The adherence rate (AR) was determined using a telephonic pill count combining information from the patient's file and dispensing data. Patients filled out a questionnaire including Medication Adherence Rating Scale (MARS), side effects, quality of life (EORTC QLQ-C30), attitude towards disease (Brief IPQ) and medication (BMQ) and the satisfaction about the information (SIMS).

Results: Of 79.5% of 166 patients using capecitabine (n = 64), dasatinib (5), erlotinib (3), imatinib (20), lenalidomide (25), nilotinib (5), sunitinib (14), temozolomide (23) and thalidomide (7) were adherent. The mean AR was 98.8% (range:70.0–121.4) with 22 patients (13.3%) showing an AR < 95% and 12 patients (7.2%) showing an overuse > 105%.

The following variables were tested univariate for all patients: gender, age, hospital, indication (hematologic/oncologic), dosing regimen (continuous/cyclic), duration of use (< 1 year/≥1 year), status of use (past/current), partner status, education, work, BMQ and Brief IPQ. There was a significant relationship ($p < 0.05$) with: indication OR 3.3 (CI95%:1.5–7.3), dosing regimen OR 4.9 (CI95%: 2.2–10.9), partner status OR 3.5 (CI95%:1.5–8.3), education OR 2.7 (Cl95%:1.2–6.5) and Brief-IPQ OR 1.04 (CI95%: 1.001–1.07). For the current users we also tested: side effects, MARS, SIMS and QoL. Only MARS (25/ < 25) was significant; OR 0.31 (CI95%:0.10–0.95). In a multivariate analysis significant ($p < 0.05$) risk factors for suboptimal adherence for all patients were: partner status OR 17.0 (CI95%:3.5–82.0), dosing regimen OR 16.1 (CI95%:3.8–68.4) and Brief-IPQ OR 1.07 (CI95%:1.01–1.13).

Conclusions: The mean adherence was 98,8%. Most patients were optimal adherent (AR 95–105%) However 20,4% had a suboptimal adherence. Patients living alone and using an anticancer agent with a continuous dosing regime (often an haematological agent) are most at risk for non-optimal adherence.

995. Adherence, Exposure and Patient-Reported Side Effects of Erlotinib Used in Daily Practice

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Background: Diarrhea and skin rash are the most common side-effects of erlotinib. Higher exposure to erlotinib has been associated with skin rash. Moreover, (EGFR WT) patients who experience a high grade of skin rash might experience prolonged survival. Adherence influences the exposure to erlotinib. It is not known how adherence, exposure and side-effects are related to each other in the NSCLC treatment with erlotinib.

Objectives: To study the relationship between adherence, exposure and self-reported side-effects of erlotinib used in daily practice.

Methods: A multicenter prospective observational cohort study in which NSCLC patients starting treatment with erlotinib were followed for 16 weeks. Blood samples were collected in week 4 (T1), 8 (T2) and 16 (T3). Plasma concentrations of erlotinib were analyzed by a validated liquid chromatography MS/MS. Demographics and side-effects were measured by a questionnaire at the start (T0), T1, T2 and T3. Adherence was measured using a medication event monitoring system. Patient groups were compared by means of Mann Whitney tests.

Results: Of 75% of the 62 patients (54% male, mean age 61 ± 8.2 years) discontinued erlotinib use within 16 weeks, mainly due to disease progression (n = 26) and side-effects (n = 8): 46 patients reached T1, 26 patients T2 and 14 patients T3. This yielded 84 observations of 46 patients for PK analysis. Mean adherence in the week prior to blood sampling (percentage of days covered, PCD) was 97% (range 83–100%). Patients with 100% PCD had a shorter period of use than patients < 100% PCD (54 ± 28 resp. 90 ± 35 days, $p = 0.001$). Patients with skin rash had a higher AUC than patients without skin rash (28.2 ± 11.6 vs. 40.6 ± 16.3 mg*h/L, $p = 0.021$). There was a trend that patients who "did not feel well" had a higher AUC than patients that didn't experience this mood ($p = 0.08$).

Conclusions: In daily practice there was a high dropout during the first weeks of treatment with erlotinib. Exposure was higher in patients who experienced skin rash. Because the appearance of skin rash may be related to the effectiveness of treatment in EGFR WT patients, it might be useful to measure erlotinib plasma levels in patients that don't experience skin rash.

996. Cytostatic Drug Prescribing: Analysis of a South African Claims Database

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Background: African states will account for more than a million new cancer cases per year out of a total of 16-million cases worldwide by 2020 according to the WHO. Although cancer drugs account for < 15% of total health care expenditure, these drugs are expensive. Limited studies could be found on the prescribing patterns of cytostatic drugs in South Africa.

Objectives: To determine the prescribing patterns of cytostatic drugs to a private sector patient population using a claims database of a South African medical aid administrator.

Methods: A cross-sectional, retrospective drug utilization study was conducted on a prescription database of a medical aid administrator for 2010. A total of 4,111 prescriptions for drugs classified under ATC Code L were prescribed. All records for cytostatic drugs and implant seeds were extracted for analysis. No diagnoses were available.

Results: A total of 2,806 cytostatic drugs were prescribed to 362 patients at a total cost of R2833876 during 2010. The average age of patients was 51.47 years, 52.21% of patients were females, and 49.72% of patients were between 40 and 59 years of age. Patients received on average of 7.75 (SD = 6.93) cytostatic products during the

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year with patients between 60 and 69 years receiving the highest average (10.70 products). The average cost per cytostatic prescription was R1009.93 (SD = R3552.16). Forty-two different active ingredients were prescribed, mostly infusions, powders for reconstitution and injections. Methotrexate was the most often prescribed active ingredient (55.60%), followed by cyclophosphamide (7.52%), doxorubicin (5.20%), paclitaxel (4.42%) and hydroxyurea (3.31%). Although most prescriptions were dispensed by pharmacies (84.96%), most patients (60.62%) were referred by general medical practices or radiation oncologists. Other drug classes frequently prescribed to these patients were drugs acting on blood and blood-forming organs (ATC Code B) and the central nervous system (ATC Code N).

Conclusions: More studies are needed to cast light on drugs prescribed for specific types of cancer and the cost of treating different types of cancer. The importance to include diagnoses in claims databases is evident from this study.

998. Drug Use Study of Doxorubicin Using Japanese Claim Data of Inpatients

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Background: Doxorubicin is one of the traditional anticancer drugs and widely used in the treatment of lymphoma, breast cancer, digestive cancer and other various cancers. However, this drug sometimes causes cardiotoxicity that may lead to a form of congestive heart failure. It is known that risk of cardiotoxicity greatly increases with the use of higher doses of Doxorubicin, especially more than 500 mg/m^2 in total dosage. Prescribed dosage of Doxorubicin and incidence proportion of cardiotoxicity in recent cancer patients has not been investigated well. Thus, Drug Use Study of Doxorubicin was performed using the claim data including detailed information about cancer stages and prescriptions during hospitalization.

Objectives: To investigate Doxorubicin use and the risk of cardiotoxicity during hospitalization using Japanese claim data of inpatients.

Methods: The Japanese claim data of inpatients called Diagnosis Procedure Combination (DPC) data was used in this study. The owner of these data, a DPC system vender, performed all analysis by following the protocol prepared by PMDA. The base population for this analysis included about 0.9 million of patients hospitalized in 170 hospitals during July 2010 to June 2011. The targeted population was defined by prescription of Doxorubicin at least one time during that period. In analysis, distribution of patient demographics, the risk factor of cardiotoxicity (total dosage > 500 mg/m^2) and the incidence proportion of cardiotoxicity were calculated.

Results: Among 0.9 million of the base population, 3,942 patients were prescribed Doxorubicin during the study period. Their median age was 66 years and their median length of hospital stay was 22 days. Only 8 patients (0.20%) were prescribed Doxorubicin more than 500 mg/m^2. Seventy-seven patients (2.0%) were given any diagnoses of cardiotoxicity, however, none of patients among these cases was prescribed Doxorubicin more than 500 mg/m^2.

Conclusions: This study showed that the number of patients prescribed Doxorubicin more than 500 mg/m^2 was very limited. Although the dosage was not immoderate, some patients were given cardiotoxicity diagnoses.

999. Gadolinium Prescribing Trends – The Effect of Regulatory Action

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Background: Gadolinium-containing agents are associated with a risk of nephrogenic systemic fibrosis (NSF), first observed in 2006. Regulatory advice was communicated in August 2007 advising healthcare professionals that Omniscan and Magnevist should not be used in patients with severe renal dysfunction. Following a drug class review in November 2009 by the European Committee for Medicinal Products for Human Use (CHMP), the NSF risk classification was updated to highlight risk. Further regulatory advice on how to minimise risk of NSF in vulnerable patient groups was communicated to healthcare professionals in January 2010.

Objectives: To assess the changes in the use of gadolinium-containing drugs over time in light of regulatory action.

Methods: The volume stock of gadolinium-containing drugs into UK hospital pharmacies between 01/2006 and 03/2011 were extracted from IMS MIDAS database. The usage data are presented as number of vials (or pre filled syringes) every quarter, stratified by product name.

Results: During 2006 and 2007, the gadolinium-containing contrast agents used most often were Magnevist and then Omniscan; however a significant drop in usage was seen with these two drugs over the past 5 years. During 2007Q2 and 2008Q2, the number of vials issued for Magnevist and Omniscan dropped by 33% and 74% respectively. Between 2009Q4 and 2010Q4, the number of vials dropped again by 32% and 44%. In comparison, Gadovist and Dotarem Gue currently classified as low risk of NSF, usage increased from 2007 onwards. Approximately 24,000 Gadovist vials and 33,000 Dotarem Gue vials were issued during the first quarter of 2011, compared to 9,000 Magnevist vials and 2,000 Omniscan vials.

The usage of MultiHance, Primovist and Vasovist remained relatively constant overall during the 5 years.

Conclusions: Over the past 5 years, the usage of gadolinium-containing contrast agents with a high risk of NSF has gradually shifted to those with a low risk of NSF. By 2011, Gadovist and Dotarem Gue were the most issued gadolinium-containing contrast agents. It is possible regulatory decisions and communications contributed to the significant drop in usage of high risk Omniscan and Magnevist agents in 2007 and 2010.

1000. The Pattern of Use Human Immunoglobulins in the Clinical Centre University of Sarajevo (CCUS)

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Background: Human immunoglobulins (J06BA02) are important drugs for pharmacotherapy of different clinical indications.

Objectives: The goal of the paper was to analyze pattern of using human immunoglobulins in the CCUS during the period of 6 months (2011).

Methods: Descriptive and retrospective study. Analysis encompassed the period of 6 months (July–December) for year 2011. We made analysis of utilization and dosing of human immunoglobulins.

Results: We identified 44 patients treated with human immunoglobulins. Age of patients were from 0 to 82 years (M = 27.54, SD = 24.56), 22 females (50%). Most of patients were children (n = 18, 41%), than adults from clinic of hematology diseases (n = 11, 25%) and clinic of neurology diseases (n = 5, 11%). We treated mainly patients with sepsis and infections (n = 7, 16%), myeloma multiplex (n = 5, 11%), primary immunodeficiencies (n = 4, 9%) and immune thrombocytopenic purpura (n = 3, 7%). Daily doses of human immunoglobulins were from 1.5 gram/daily (Rh incompatibility) to 90 grams/daily (immune thrombocytopenic purpura).

Conclusions: Through analysis of patterns of using human immunoglobulins we have recorded big differences in dosing and duration therapy with human immunoglobulins in CCUS in relation to the recommendations from Clinical Guidelines for Immunoglobulin Use (Department of Health, UK, 2011).

1001. Evaluation of the Process of Immunosuppressive Drug Dispensation for Renal Transplant Patients by Minas Gerais State Health Secretary at 2008

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Background: Brazil is faced with the challenge of sustaining the largest transplant public system in the world and offering drugs for maintenance of the grafts.

Objectives: The study aims to evaluate the process of immunosuppressive drug dispensation for renal transplant patients by Minas Gerais (MG) State Health Secretary.

Methods: Cross-sectional analysis using 687 patients who underwent renal transplant and receive immunosuppressive therapy in 2008, identified by registries of all patients financed by Brazil's National Health System-SUS (Component Specialized of Pharmaceutical Services), in state of MG. Data collection was performed from a computerized file and complemented by visits in the Regional Health Management (RHM). Chi-square test to compare proportions and Student t-test and Mann–Whitney test to compare means were used. The variables analyzed were related to: demographic profile, characteristics of drug dispensing (RHM, necessary proceedings to get the appraisal of the application and current status – approved, rejected or under evaluation), drug dispensed (monthly cost and prioritization in the SUS Therapeutic Guidelines and Clinical Protocols-TGCP). The monthly cost of therapy for an adult of 70 kg was calculated. The drug in this Guideline were classified as 1st choice (cyclosporine and azathioprine), 2nd choice (mycophenolate mofetil/sodium, tacrolimus and sirolimus) or mixed (including those of 1st and 2nd choice).

Results: Considering the number of requests, most of the drugs were classified as 2nd choice, representing an increase of at least 301% in cost compared to the 1st choice therapies. The RHM of Belo Horizonte (capital of the state of MG) dispensed 3.5 times the proportion of 2nd choice medicines and had a shorter mean time of process evaluation compared with the other's RHM. The comparisons were statistically significant.

Conclusions: The study notes the disparity between TGCP and the dispensation of immunosuppressive therapies. This indicates the importance of using methods of health technology assessment, as well as epidemiological studies, to optimize health services aiming the principles of the SUS.

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1002. Perception and Clinical Care of Depression in Breast Cancer Patients: A Survey of Oncology Practice in Japan

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Background: Depressive disorder is a common mental illness in breast cancer patients. A recent study in Japan reported the prevalence of adjustment disorder or major depression in relapsed breast cancer patients at 42%. Yet, this prevalence is likely underestimated due to the lack of trainings among oncologists. Moreover, treatment choice by oncologists is unknown.

Objectives: To investigate the current perception and clinical practice of oncologists in relation to depression in breast cancer patients.

Methods: Self-reported questionnaires were sent to 352 oncologists who were members of the Public Health Research Foundation in Japan. The survey contains 11 categories to elicit the perception and identification of mental illnesses in patients, diagnostic procedure, and details of antidepressant prescribed. Logistic regression was used to explore the association of physicians' characteristics and management of depression in breast cancer patients.

Results: Survey response rate was 31.3% (n = 110). Nine in 10 perceived the prevalence of depression among breast cancer patients to be $<20\%$. In fact, about half believed the proportion was $<5\%$. These oncologists also perceived low prevalence of anxiety (Spearman ($\rho = 0.53$, $p < 0.01$) and sleep disorder (0.44, $p < 0.01$). However, the number of psychiatric referrals was not related to any perceptions. Benzodiazepines (BZDs) were most frequently prescribed (41.5%) despite known dependency, followed by Selective Serotonin Reuptake Inhibitors (SSRIs) (31.9%). Choice of BZDs was significantly associated with the experience of oncologists. (Odds Ratio = 8.04, 95% confidence interval = 2.62–24.7), safety of drug (6.27, 1.99–19.71). Contrarily, prescription of SSRIs was associated with effectiveness of drug (7.07, 1.90 –26.39).

Conclusions: Low awareness of depression in breast cancer patients was common among oncologists. Quality of care varies by doctors. There is a need to improve awareness, identification and management of mental illnesses.

1003. Linking a Voluntary Patient Registry with US State Cancer Registries for Signal Detection

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Background: Regulatory commitments to monitor long-term outcomes such as cancer are increasing in both the US and Europe. Linking data from patients exposed to a medication of interest with cancer registries is one approach to monitoring for potential signals. The ongoing Forteo Patient Registry, initiated in 2009, can provide insights for patient recruitment and cancer registry linkages.

Objectives: To describe patient recruitment methods, cancer registry linkage status, and progress of the voluntary Forteo Patient Registry, designed to estimate the incidence of osteosarcoma in patients who have received treatment with Forteo.

Methods: Patient enrollment is tracked quarterly by method of recruitment (i.e., where patient obtained enrollment form). For 12 years, an annual linkage will be performed by all participating state cancer registries using a standardized linkage algorithm with the Forteo Patient Registry database. Linkage variables include name, birth date, sex, address, telephone number, race, ethnicity, and last 4 digits of social security number.

Results: As of December 2011, a total of 22,105 US patients were registered. The distribution by method of recruitment was medication packaging (63%), starter kit (24%), study toll-free number (6%), physician tear pad (2%), patient brochure (2%), direct pharmacy mail (2%), and study website (1%). In September 2011, a total of 37 state cancer registries covering 85% of the US population participated in the second annual linkage, linking 16,365 patients from the Forteo Patient Registry with 961 adult osteosarcoma cases diagnosed since January 1, 2009. No matches among Forteo users were identified.

Conclusions: Including information about this voluntary patient registry in product packaging has been the most frequent pathway for patient recruitment to date. Linking with a large proportion of US state cancer registries is feasible but requires significant effort and resources on the part of the researchers and cooperation by multiple individuals at each participating cancer registry.

1004. Second Malignancies (SM) among Multiple Myeloma (MM) Patients Exposed to Bortezomib (Btz) and Other Treatments: An Analysis of the US SEER-Medicare Linked Database

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Background: Second hematologic malignancies occur at a higher rate among MM patients compared to the general population. Although alkylating agents has been suggested to play a role, underlying causes remain unknown. Novel agents are extending survival, and, as

noted in other cancers, SMs may be increased. Data from Phase III studies suggest that patients treated with lenalidomide with prior exposure to melphalan may have an increased risk of SM compared to placebo. However, the contribution of other agents has not been well characterized.

Objectives: To determine the incidence of SM by Btz treatment status, and quantify risk of SM comparatively by treatment while adjusting for potential confounders.

Methods: We identified newly diagnosed MM patients ≥66 years in the US SEER-Medicare database, from January 2000 through December 2007. Unadjusted incidence rates (IRs) were calculated for all SMs, hematologic and solid tumors. Cox proportional hazards models were developed to determine the effect of Btz and other treatments on the incidence of SM, while controlling for major risk factors.

Results: Of 5,800 treated MM patients were identified; 1,663 had exposure to Btz. Btz patients were more likely to be male, younger, have had a stem cell transplant, and have had multiple lines of therapy. Of 188 (31 Btz) patients developed a SM, including 157 (27 Btz) solid tumors and 31 (4 Btz) hematologic malignancies. The overall IR of SM was 2.2 per 100 person-years, with no difference between Btz exposure status. After adjustment, there was no statistical difference in risk for patients exposed to Btz compared to unexposed (HR:0.84, 95% CI:0.56–1.26). Patients exposed to other standard therapies (non-Btz, non-alkylating) had an increased risk of SM compared to those unexposed (HR:1.58, 95% CI:1.17–2.14). Risk was decreased among females compared to males (HR:0.66 95% CI:0.49–0.88).

Conclusions: This study provides additional evidence to contribute to understanding the safety profile of Btz, and is consistent with prior clinical trial and post-marketing surveillance studies.

1005. Health Care Utilization (HCU) by Breast Cancer (BC) and Non-Hodgkin Lymphoma (NHL) Patients (pts) with Chemotherapy (CT) Induced Febrile Neutropenia (FN) in the Netherlands

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Background: CT-induced FN can result in reduced CT delivery, unplanned hospitalizations, and increased mortality risk.

Objectives: Changes in clinical practice warrant investigation of current resource use and economic cost of FN; therefore, we studied FN-related HCU among BC and NHL pts.

Methods: Data from incident adult cancer pts with a primary hospital discharge diagnosis for BC or NHL from 1998 to 2007 were obtained from the PHARMO Record Linkage System, including pharmacy, hospital and clinical lab data. Eligible pts had ≥12 months medical history available and received CT ≤6 months after cancer diagnosis. Pts developing FN ≤6 months after first CT (FN pts) were matched 1:2 on gender, birth year, and CT regimen to pts without FN (non FN pts). HCU data (hospitalizations, medical procedures, drug use [number dispensed]) was tallied from entry date (date of FN or matched date for non FN pts) for up to 3 months. Statistics are descriptive with crude odds ratios (OR).

Results: Of 80/1,033 BC pts (8%) developed FN (all were matched). Of 95/486 NHL pts (20%) developed FN (89 were matched). More FN than non FN pts were hospitalized in the 1st month after the entry date: BC 73% vs. 14% (OR = 23.0 [95% CI 8.3–63.7]); NHL 78% vs. 33% (OR = 7.6 [3.9–15.1]). These differences were mainly due to FN-related hospitalizations (BC 55% vs. 1%, NHL 47% vs. 4%). FN pts also had a longer mean length of stay per all-cause hospitalization: BC 4.6 vs. 1.9 days; NHL 10.1 vs. 3.0 days. In the 1st month after entry date, the mean number of total drugs dispensed per pt was higher in FN pts than non FN pts (BC 5.8 vs. 3.1, NHL 8.5 vs. 3.6); use of anti-infectious agents was higher (BC 99% vs. 11%, NHL 96% vs. 20%), as was number of

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other non-CT drugs. More FN than non FN pts had medical procedures (BC 14% vs. 3%, NHL 13% vs. 8%). HCU differences between FN and non FN pts were maintained after 3 months.

Conclusions: This study confirms the high resource utilization currently associated with FN, based on BC and NHL pt data from the Netherlands. Reduction of FN may improve quality of life and save resources.

1006. Detection of Cerebral Infarction Associated with Oral 5-Fluorouracil S-1 and Other Fluoropyrimidines Using a Hospital Database

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Background: S-1, the combination of tegafur, gimeracil and oteracil potassium, is an oral fluoropyrimidine indicated for gastric and colorectal cancer and other carcinomas. There have been a few spontaneous reports of the occurrence of cerebral infarction (CI) in patients prescribed with S-1, however, the possibility for the association of the CI occurrence with S-1 has not been clarified.

Objectives: The aim of this study was to detect the CI occurrence after chemotherapy of S-1, UFT (combination of oral tegafur and uracil) and 5-FU injection using a hospital database.

Methods: A cohort study of the patients of Hamamatsu University Hospital, Japan was designed. An association between S-1 prescription and CI occurrence was searched from all in- and out-patients from January 2008 to December 2010. CI was searched by ICD-10 code of I63, and confirmed by a diagnosis based on computed tomography (CT) or magnetic resonance imaging (MRI). The cases' risk factors of CI were surveyed; age, sex, smoke, alcohol drinking, complication of hypertension, DM, lipid disorders and history of cardiac disease. An association between prescription of UFT or 5-FU and CI was also searched. Incidence rate and 95% confidence interval of CI after these drugs were estimated.

Results: In the research period, S-1 was prescribed in 577 patients. Eight patients had a diagnosis record of CI within 2 months after the first prescription of S-1. By the diagnostic imaging, four patients were confirmed as the cases with CI after S-1 therapy (0.69%, 95% CI: 0.27–1.77%). CI occurred in 28–32 days from the start of S-1. All cases were male and 59–79 years old. Although two cases had a history of smoking, all cases had no other risk factors for CI. UFT was prescribed in 216 patients, and no patients had a diagnosis record of CI within 2 months after the first prescription of UFT. 5-FU was prescribed in 216 patients, and one patient was confirmed as a case with CI after 5-FU therapy (0.46%, 95% CI: 0.08–2.58%).

Conclusions: CI occurrence after S-1 and 5-FU therapy was able to be detected using a hospital database and confirmed by the diagnostic imaging.

1007. Immunosuppressants Associated with Progressive Multifocal Leukoencephalopathy within the US Adverse Event Reporting System

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Background: Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system. In the last years, it has gained particular attention as an adverse drug reaction (ADR) of immunosuppressive drugs.

Objectives: To investigate the association of PML and immunosuppressants using a disproportionality analysis of spontaneous reports.

Methods: Within the US Adverse Event Reporting System, we analysed all reports of adverse drug reactions, submitted to the US Food and Drug Administration between January 1, 2004 and September 30, 2010. As cases, we identified all patients with a code for PML according to the Medical Dictionary for Regulatory Activities. Patients with other ADRs were considered as non-cases. All patients were classified as either exposed or not exposed to all immunosuppressants (L04) according to the Anatomical Therapeutic Chemical classification system. For all drugs, we calculated reporting odds ratios (ROR) of PML compared to all other drugs using logistic regression analysis. In addition to crude estimates, we conducted a multivariate analysis including all immunosuppressants reported with PML. A signal for a drug was defined by the following: a ROR > 2, $p < 0.05$ and ADR reports for the drug in at least three PML cases.

Results: In total, N = 1,998,513 patients were eligible for analysis. N = 726 were PML cases, N = 1,997,787 had another ADR. The majority of PML cases were reported in patients with lymphoproliferative disorders or leukemias (33.3%) and autoimmune disorders (29.9%). In univariate analyses, we found a signal for nine out of 34 immunosuppressants (azathioprine, cyclosporine, efalizumab, leflunomide, methotrexate, mycophenolate mofetil, natalizumab, sirolimus and tacrolimus). In the multivariate analysis, a signal was no longer present for cyclosporine and sirolimus.

Conclusions: Our study revealed signals of PML for a substantial number of immunosuppressants, including some drugs less considered so far, e.g., leflunomide or azathioprine. Further research is needed to quantify possible interactions and the influence of individual drugs.

1008. Relative Risk of Myeloid Neoplasms in Patients with Autoimmune Disease

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Background: Myeloid neoplasms (MNs) are a subset of hematologic malignancies that include myelodysplastic syndromes (MDS), chronic myeloproliferative disorders (CMPD), and acute myeloid leukemia (AML). It has been suggested that abnormalities of the immune system may be responsible for MNs, but it is unknown if specific autoimmune disorders increase the risk. Previous studies have been unable to separate the effects of autoimmune disease from that of the treatment for the disease on the risk of MNs.

Objectives: To estimate the effects of a history of autoimmune disease, both with and without exposure to treatments, on the risk of MNs, by MN subtype.

Methods: We conducted a nested case–control study using the General Practice Research Database. Incident cases of MNs were identified and up to four controls were matched to each case. Exposure was defined as a diagnosis of a specified autoimmune disorder prior to the index date and subclassified by types of treatments received. We used conditional logistic regression to estimate the crude and adjusted ORs for MNs, by subtype, compared with patients with no history of autoimmune disease.

Results: We identified 3,196 cases (849 MDS, 1,924 CMPD, 398 AML and 25 unknown) who met our inclusion criteria. There was a slightly increased risk of MDS in patients with any autoimmune disease (OR 1.5, 95% CI 1.1, 2.0). The risk of MDS in patients with 10 + year history of autoimmune disease was greater: OR 2.1, 95% CI 1.4–3.2. The increased risk of MDS was present in both treated (OR 1.2 95% CI 0.8–1.9) and untreated (OR 1.7 95% CI 1.2–2.5) patients. There was an increased risk of AML in patients who were treated with multiple treatments (OR 3.1 95% CI 0.8–12.0), but not in untreated patients (OR 0.8, 95% CI 0.4–1.5). There was no effect on the risk of CMPD.

Conclusions: Both the underlying autoimmune disease and treatment for the disease increased the risk of MDS, and there is evidence for a potentially increased risk of AML in treated patients. Neither autoimmune disorders nor their treatment appear to be associated with an increased risk for CMPD. These data will aid in the interpretation of other studies where treatment information is not available.

1009. Chronic Comorbidities and Chemotherapy-Induced Febrile Neutropenia (FN) in Breast Cancer Patients

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Background: Clinical guidelines recommend granulocyte-colony stimulating factors (G-CSF) be used in cancer patients when FN risk is > 20%. Chemotherapy regimen is a key determinant of FN risk, but patient characteristics such as chronic comorbidities may modify this risk further.

Objectives: To determine the association of chronic comorbidities and FN in breast cancer patients.

Methods: Incident breast cancer cases who received chemotherapy were identified from Kaiser Permanente Southern California (2000–2009). Those who had prophylactic G-CSFs or dose-dense chemotherapy were excluded. Comorbidities, including cardiovascular, liver, renal, and metabolic disorders, were assessed prior to cancer diagnosis, and identified by ICD-9 codes or disease registries. FN was assessed only in the first chemotherapy cycle, and identified by absolute neutrophil count (ANC), ICD-9 codes for neutropenia and fever, or hospitalization with bacterial/fungal infection. A separate logistic regression model was used to estimate the propensity score for each comorbidity of interest; covariates included patient characteristics and other comorbidities. A Cox model, adjusting for the propensity score, was used to determine associations between each comorbidity and FN. We also evaluated Cox models that additionally adjusted for cancer stage, baseline ANC, chemotherapy regimen, and dose reduction.

Results: Of the 7,165 breast cancer patients who received chemotherapy, the mean age was 55.4 years, and the majority had localized (46%) or regional (49%) disease at diagnosis. There were 337 (4.7%) patients that had FN in the first chemotherapy cycle. Congestive heart failure (HR = 3.2, 95% CI [1.3–6.4]), osteoarthritis (HR = 2.0 [1.4–2.8]), previous cancer (HR = 4.2 [1.6–8.7]), and thyroid disorder (HR = 1.7 [1.1–2.3]) were statistically significantly associated with an increased FN risk. These estimates were similar to those that also adjusted for cancer stage, ANC, chemotherapy regimen and dose reduction.

Conclusions: Our findings suggest that several chronic comorbidities may be associated with FN risk in the first chemotherapy cycle among breast cancer patients not already receiving prophylactic G-CSFs.

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1010. Liver Enzyme Elevations in Patients with Solid Tumors

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Background: Liver dysfunction is a known complication in cancer, but little is known about the epidemiology of hepatotoxicity in cancer patients.

Objectives: To estimate the incidence of liver enzyme elevations in patients with solid malignancies.

Methods: Adult patients with an initial diagnosis of one of 11 types of solid tumors between January 2000 and April 2008 were identified from outpatient oncology clinic data in the Varian Medical Oncology EMR database. The cohort included patients with normal liver enzyme levels at baseline and at least one follow-up liver function test. Incidence rates of liver enzyme elevations in the follow-up period were calculated overall, and by chemotherapy exposure status. Time to the first elevation and time to return to normal after an elevation were also estimated. A Poisson regression model sought predictors of any liver enzyme elevation from among baseline demographic and disease factors, as well as time on and off chemotherapy during follow-up.

Results: The cohort of 11,452 patients had a mean age of 62 years at diagnosis; 66.1% were female, and most had breast, lung, or colorectal cancer. Of 57.4% of patients experienced a liver enzyme elevation, at a median of 140 days after initial cancer diagnosis. The incidence of any elevation was 64.60 cases per 100 person-years (95% confidence interval [CI]: 49.81–82.40) and was considerably higher during periods of chemotherapy use than non-use (263.11 and 44.13 per 100 person-years, respectively). Most patients with a liver enzyme elevation during chemotherapy showed a return to normal levels without stopping chemotherapy. Concomitant ALT and bilirubin elevations suggestive of Hy's Law was rarely found, occurring in $<1\%$ of each cancer group except for melanoma, soft tissue sarcoma, and gastric cancer ($<2\%$ each). Poisson regression analysis showed that chemotherapy exposure was strongly associated with increased risk of liver enzyme elevation (rate ratio: 4.98; 95% CI: 4.69–5.29).

Conclusions: More than half of the patients with solid tumors were found to have liver enzyme abnormalities after cancer diagnosis. Chemotherapy use was associated with frequent but transient elevations.

1011. Incidence of New-Onset Hypertension in Cancer Patients

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Background: Reports of hypertension as an adverse event with cancer treatment need to be considered within the context of the natural history of hypertension in cancer patients.

Objectives: To estimate incidence rates of new-onset hypertension in patients with solid malignancies.

Methods: Adult patients with breast, lung, colorectal, prostate, head and neck, melanoma, ovarian, renal, connective/soft tissue, gastric, and cervical cancer were identified from the Varian Medical Oncology electronic medical record database from US outpatient oncology practices. Patients were normotensive for 30 days before first cancer diagnosis and had >1 blood pressure (BP) measurement after diagnosis. Incidence rates (IRs) of hypertension, categorized as moderate, severe, and crisis levels, were calculated overall and separately for periods of chemotherapy exposure and non-exposure. Cox proportional hazards regression was used to develop separate predictive models for moderate or higher, severe or higher, and crisis-level hypertension.

Results: Of 25,090 qualifying cancer patients, mean age was 61 years. The most common tumor types were breast (36.1%), lung (25.6%), and colorectal (16.0%). IRs of hypertension decreased with increasing severity level, from 27.3 cases per 100 person-years (PY) for moderate, 12.4/100 PY for severe, and 2.8/100 PY for crisis-level hypertension. Across all cancer types, adjusted Cox models found a 2- to 3.5-fold increase in risk of moderate hypertension associated with chemotherapy exposure. Severe and crisis-level hypertension showed greater variability in risk by type and line of therapy but still indicated an overall increase with chemotherapy exposure.

Conclusions: Although new-onset moderate hypertension was relatively common, crisis-level hypertension occurred in $<5\%$ of patients with solid tumors. Chemotherapy use appeared to be associated with elevated risk of hypertension at each severity level, but BP monitoring was more frequent during chemotherapy. These results provide data on the natural history of hypertension in cancer patients.

1012. The Changing Pattern of Aflatoxins Exposure and Its Risk of HCC in Egypt

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Background: Aflatoxins are important food-borne mycotoxins and potent liver carcinogens that frequently con-

taminate cereals in developing countries such as Egypt. The burden of aflatoxins exposure has been dramatically increased during the past 10 years.

Objectives: This study aims to determine prevalence of aflatoxin exposure in either healthy people or patients in Egypt.

Methods: A systematic search from 1st January 2002 to 1st January 2012 of MEDLINE, Science Direct and World Health Organisation databases was undertaken for relevant articles using the following terms (aflatoxin and Egypt), (aflatoxicosis and Egypt), (mycotoxin and Egypt), (aflatoxin prevelance and Egypt). We calculated mean prevalence for aflatoxin exposure among the populations of interest and examined differences in prevalence by descriptive features, including age, year and geographic region.

Results: Prevalence of aflatoxin b1 exposure was 91% and 40% among cirrhotic and hepatocellular carcinoma (HCC) patients, respectively. Incidence of aflatoxins exposure in male was higher than female (82.5% vs. 17.5%). Aflatoxins exposure has been determined in maternal milk as aflatoxin (M1) in 49.6%, although aflatoxin b1exposure had been 63% and 38% in infants and children, respectively.

Conclusions: The findings of this study document the different level of aflatoxin exposure at healthy people or patient either in male or female at different age. This population-based registry offers the opportunity for careful representative studies for afltoxins exposure. It can be concluded that significant increase of aflatoxins exposure is one of the major risk of HCC in Egypt and need for feasible intervention strategy to reduce and prevent afltoxins exposure as well as gama radiation for cereals, early monitoring for the highly risk people.

1013. Preliminary Results from the Pilot Phase of a Chinese Hospital-Based Epidemiologic Study of Stomach Cancer (CHESS): Tumor Characteristics, Treatment Patterns and Clinical Outcomes

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Background: Stomach cancer (SC) is the fourth most common malignancy in the world and the highest incidence rates are found in Asia. Although the diagnosis and treatment of SC have improved over the last two decades in China, clinical and survival data are limited.

Objectives: This epidemiologic study aims to collect data and describe tumor characteristics, treatment patterns and outcomes in SC patients (pts), and support future benefit-risk assessments on SC therapies.

Methods: This is an observational cohort study designed to follow pts with stomach or gastroesophageal junction cancer seen at the General Surgery Department of a leading hospital in China – Shanghai Zhongshan Hospital. We describe an initial pilot study involving retrospective medical chart review of pts seen at the department (dept) from January 2009 to March 2011 to assess feasibility of data collection tool and extent of available data. Proportions, means, medians and ranges were used.

Results: A total of 110 SC pts (68% male) were included in this pilot study with a median age of 61 years. Seventy-seven percent of the pts lived in urban areas and 23% lived in rural areas. Since pts were identified through the surgical dept, all pts received surgery (20% laparoscopic and 80% laparotomy). Ninety-two percent of pts achieved a R0 resection. The majority of resectable SC pts presented with a tumor that had already invaded the muscularis. Postoperative pathology results indicated that 15.7% of pts were stage IA, 6.5% IB, 6.5% IIA, 6.5% IIB, 16.7% IIIA, 14.8% IIIB, 24.1% IIIC, and 9.3% IV according to 7th American Joint Committee on Cancer staging system. Severe dysplasia was diagnosed in 2%; the remaining 98% were cancer.

Conclusions: The pilot phase of this study was successfully completed. A larger SC cohort which may include up to 2000 pts (identified both retrospectively and prospectively) from this hospital is planned. Surgery/pathology and medical treatment (e.g., chemotherapy) data will be collected and may aid in improving screening, diagnosis and treatment strategies for SC patients.

1014. Epidemiology of Metastatic Pancreatic Cancer in the United States and Selected European Countries

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Background: Pancreatic cancer is the 4th and 5th leading cause of cancer death in the US and the European Union, respectively. Overall 5-year survival is 5% and median survival is about 6 months for metastatic disease.

Objectives: Compile epidemiological data on metastatic pancreatic cancer and describe incidence, prevalence, and survival in the US, Germany, France, UK, Spain, and Italy.

Methods: We conducted an electronic literature search to identify published population-based epidemiological studies. We also compiled epidemiological data from 4 population-based registries: US SEER, the European Cancer Observatory (ECO), the European Cancer Registry (EUROCARE), and the Scottish Cancer Registry (SCR).

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Results: Age-adjusted incidence of pancreatic cancer in the US was 9.1 per 100,000 for all stages and 4.8 per 100,000 for metastatic disease as reported by SEER. Age-adjusted incidence rates for all stages in Europe ranged from 8 to 10.6 per 100,000 in Spain and Germany, respectively, as reported by ECO. Ten-year limited duration prevalence in SEER was 2.2 per 100,000 for cancers classified as metastatic at diagnosis. Prevalence rate of pancreatic cancer in Scotland at end of 2007 was 8.3 per 100,000 based on diagnoses for all stages made in the previous 20 years (SCR). Percentage of patients presenting with metastatic disease at diagnosis in the US ranged from 33.4% to 54%, although the fraction with unknown stage was as high as 34.1%. US SEER data for metastatic disease report 1-, 2-. and 5-year survival rates of 11.2%, 3.0%, and 0.7%, respectively. A Spanish study reported 1-, 2-, and 5-year survival rates of 17%, 4.2%, and 0.6%, respectively, for all stages. According to EUROCARE data for all stages, 1-year survival ranged from 10.7% in Northern Ireland to 22.8% in France, and 5-year survival ranged from 2.1% in Northern Ireland to 5.8% in France.

Conclusions: Survival data for metastatic pancreatic cancer are available in the literature, but incidence or prevalence rates are not. The SEER registry reports incidence, prevalence, and survival for patients with metastases at time of diagnosis. European registries report epidemiological data without breakdown by disease stage.

1015. Renal Impairment after Chemotherapy in Lung (LC), Colorectal (CRC), and Breast Cancer (BC) Patients (pts) from the Henry Ford Health System (HFHS) Tumor Registry

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Background: Renal impairment is a common comorbidity in cancer pts. It can delay excretion and alter metabolism of anticancer drugs leading to further renal toxicity.

Objectives: The objective of this study was to determine the proportion of pts with renal impairment, defined as the presence of proteinuria (PR), acute kidney injury (AKI), or chronic kidney disease (CKD), after chemotherapy (chemo) initiation.

Methods: LC, CRC, and BC pts newly diagnosed between 2000 and 2007 (regardless of prior renal status) were identified using the HFHS tumor registry, with follow-up through March 2009. AKI was defined based on RIFLE (severity categories only) using lab data within 1–7 days after chemo initiation. CKD was defined based on NKF-KDOQI criteria and lab data up to 1 year after chemo initiation. Proteinuria was defined as protein/creatinine >30 mg/g within 3 months after chemo initiation. Descriptive statistics include proportions stratified by renal impairment status (yes, no) at cancer diagnosis.

Results: We identified 1,896 LC, 1,088 CRC, 1,611 BC chemo treated pts. Median age for all pts was 66 years. For LC and CRC, 56% and 51% were men, respectively. The proportion of pts with renal impairment after chemo by tumor type was the following: LC (AKI = 23.4%; CKD = 48.2%; PR = 0.4%); CRC (AKI = 20.3%; CKD = 55.7%; PR = 0.1%); BC (AKI = 7.8%; CKD = 63.9%; PR = 0.6%). Pts with pre-existing renal impairment at cancer diagnosis were more likely to have impairment after chemo (LC: AKI 19.8% vs. 33.4%, CKD 27.5% vs. 58.4%; CRC: AKI 17.5% vs. 38.4%, CKD 23.3% vs. 71.4%; BC: AKI 6.8% vs. 15.3%, CKD 29.5% vs. 79.1%).

Conclusions: In LC, CRC, and BC pts, the proportion of pts with renal impairment after chemo initiation was high. Extent of renal impairment, especially AKI, appears to be associated with tumor type. Older age, as in this HFHS cohort, is associated with higher prevalence of CKD. Renal function should be closely monitored, particularly among pts with pre-existing renal impairment, and preventive measures implemented to minimize further toxicity after treatment.

1016. Epidemiology of Cardiovascular Diseases in the General and Cancer Populations

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Background: Cardiovascular (CV) diseases have been prevalent in the general population; however, population-based studies quantifying the epidemiology of different CV diseases in the cancer population have been limited.

Objectives: To estimate the incidence rates, prevalence and trend of five different CV diseases (coronary heart disease, arrhythmia, heart failure, myocardial disorder, and pericardial disorder) among cancer patients relative to the general population in a large US insurance database.

Methods: Thomson Reuter's MarketScan Database from January 2004 to December 2009 was utilized to estimate the incidence rate and prevalence of 5 CV diseases. Cases were identified at the first diagnosis of CV diseases based on ICD-9 codes. Only one occurrence of each CV disease of interest was counted, selecting the earliest claim as the event date. Incidence rates in the cancer population (treated and untreated) were calculated by dividing the number of new cases by person-years.

Results: Prevalence of coronary heart disease, arrhythmia, heart failure, myocardial disorder, and pericardial disor-

der during 2004–2009 was 4.4%, 4.0%, 1.8%, 0.7%, and 0.2%, respectively, in the general population, whereas the prevalence in the cancer population was much higher (16.6%, 14.9%, 7.3%, 2.5%, 0.8%, respectively). Yearly prevalence of these five major CV diseases slightly increased from 2004 to 2009; however, no significant variation has been noted in the trend. Incidence rates of these five CV diseases were 5.7, 5.7, 2.7, 0.9, 0.3, per 100 person-years, respectively, in the cancer population. Incidence rates of CV diseases increased with age, and males had relatively higher incidence rates in all CV disease categories studied.

Conclusions: To our knowledge, this is the first report quantifying the epidemiology of 5 different CV diseases in a large US cancer population compared to the general population. The incidence rates and prevalence of CV diseases in the cancer population are substantial and increased with age.

1017. Comorbidity Burden and Concomitant Medication Use for Patients with Brain, Colorectal, Breast, or Ovarian Cancer in an Employer Group Database

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Background: Burden of illness of cancer patients can impact medical decision-making. Previous studies have often used composite measures to describe comorbidities and concomitant medication use for cancer patients but this may not provide sufficient detail for medical decision-making.

Objectives: The purpose of the study was to investigate the burden of illness of patients with brain, colorectal (CRC), breast, or ovarian cancer by providing detailed description of the prevalence of common comorbidities and concomitant medications.

Methods: Retrospective cohort analyses were conducted using the Thomson Reuters Marketscan Research Databases, an employer group database containing medical and pharmacy claims for 60 million lives. Patients (ages 18–64) were newly diagnosed with brain, CRC, breast or ovarian between 1/1/2001 and 12/31/2009 and did not have an ICD-9 for any cancer within 1 year prior to diagnosis. To describe patients' clinical profile, descriptive analyses (baseline and 6 months post-cancer diagnosis) were reported for comorbidities cited in literature (hypertension, diabetes, cardiovascular and respiratory disease), most frequently billed three digit ICD-9 codes, and chronic medication use (≥90 days supply during study period) grouped by therapeutic drug class.

Results: During 2001–2009, 4,667 brain, 18,180 CRC, 56,459 breast, and 3,947 ovarian cancer patients were newly diagnosed. For baseline, overall mean number comorbidities per patient was 2.3 and prevalence of hypertension was 14.1–18.2%, diabetes was 6.6–11.5%, and lipid disorder was 10.3–13.2% among the cancer types; prevalence decreased during post-diagnosis period except for diabetes in brain cancer patients. Antidepressants, cardiac drugs, and thyroid hormones were among the top 10 therapeutic drug class during the pre- and post-diagnosis periods for all four cancer types.

Conclusions: Brain, CRC, breast and ovarian cancer patients bear significant burden of illness with numerous comorbidities and medication use. Due to potential for drug-disease contraindications and drug-drug interactions, burden of illness should be considered when treating patients for their cancer.

1018. Perfil Epidemiológico, Clínico y Terapéutico Del asma en Rabat (Marruecos): Estudio Multicéntrico

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Background: El asma es un problema de salud pública, y los pacientes asmáticos representan el 7% de los pacientes que acudan a consultas en neumología.

Objectives: El objetivo de este estudio es describir el perfil clínico-epidemiológico y terapeutico del asma en la ciudad de Rabat.

Methods: Se trata de un estudio multicentrico prospectivo observacional, iniciado en sptiembre de 2010. Este estudio es sobre pacientes asmáticos, vistos en consulta en tres centros de Neumología del Hospital Universitario de Rabat.

Results: Se recopilaron 220 pacientes asmáticos entre 3,150 pacientes que acudaron a las consultas. Of 129 pacientes (58.7%) han sido vistos en consulta durante la temporada seca. El grupo de edad más frecuente fue de 30 a 35 años. El ratio del sexo fue 0.4. Se halló dificultad respiratoria en todos los pacientes y tos nocturna en el 30% de ellos. Existe herencia en 45% y 66% de los pacientes padecen factores endógenos (reflujo gastroesofágico) o exógenos (tabaquismo, alérgenos, clima, etc.). Se realizó espirometría en 31 caso con la cual se detectó un síndrome obstructivo reversible en nine pacientes. Se realizó radiografía a todos los pacientes. El asma está controlada o parcialmente controlada en 84,4% de los casos. El

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tratamiento de fondo fue a base de la combinación de β2-mimeticos de acción larga con corticoides en el 37.6% de los casos ó a base de corticoides inhalados en 44% de los casos. Un tratamiento adyuvante a base de antihistamínicos H1 ó de antibióticos ha sido prescrito en 75 pacientes.

Conclusions: Se deduce que el perfil del asma es similar a los otros países. En cambio existe una diferencia en su manejo. La estandarización del manejo del asma en Rabat es necesaria para optimizar los cuidados y reducir los costes.

1019. Clinical and Therapeutic Aspects in Asthma: A Multicenter Study

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Background: In Morocco asthma remains a public health problem. The implementation of a standardized management of asthma, with a good criteria cost-effective access to the majority of our patients, could improve the quality of life and lower health care costs.

Objectives: The objective of this study is to describe the clinical and therapeutic aspects of asthma in Rabat.

Methods: This is a prospective observational multicenter study still in progress relating to asthma diagnosed between in more than 3 months, seen in consultation in Rabat University Hospital's Respiratory-phtisiology Services and started in September 2010.

Results: One hundred twenty patients, aged between 17 and 64 years old with a female predominance (77.6%) were seen in consultation, 71 patients (58.7%) were recruited during the dry season (June–October). Asthma was Well Controlled in 43%, not Well Controlled in 26.6% and Very Poorly Controlled in 33.4%. The notion of family atopy was found in 79 cases (39.7%). Active smoking was found in seven patients (5.5%). Dust is the main trigger of asthma, alone or in combination with other factors: Mold, physical effort...etc. Allergic rhinitis and gastroesophageal reflux are the most encountered associated pathologies and constitute the main risk factors at the same time triggering and aggravating the disease. Chest radiography was performed in 10 cases (7.7%). and has revealed no pathological image. Spirometry, performed in 17 cases of which 17.6% are reversible. The obstructive syndrome was noted in five patients. The association beta 2 adrenergic agonists/glycolcorticosteroids was used in 37.6% of cases. Inhaled glycocorticosteroids alone were used in the treatment of bottom 44% in case of persistent asthma mild to moderate. The use of short-acting inhaled beta 2 adrenergic agonists way is recommended in all patients for the prevention of exacerbations, regardless of the level of control and long-term treatment. Adjuvant therapy was prescribed in case of associated pathology (allergic rhinitis and gastroesophageal reflux).

Conclusions: Well controlled asthma remains the predominant clinical form and inhaled glycocorticosteroids alone remains the basic treatment of choice for our patients.

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1022. Pharmacists' Management in Early Symptoms of Influenza or ENT Disorders

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Background: More and more patients directly approach their pharmacist to be adviced for flu like syndrome and ear, nose, and throat (ENT) disorders. However, little is know about this practice, with no pharmacoepidemiological data available.

Objectives: The objective of this study was to describe the clinical profile of patients who presented the early symptoms of influenza or ENT disorders and their management by pharmacists in term of dispensed treatment, clinical benefit and patient satisfaction.

Methods: We conducted a prospective observational study where randomly selected pharmacies in France from November 2010 to March 2011 were asked to include each week the first 10 patients, aged 12 years and older presenting flu-like symptoms or ENT disorder, appeared < 36 hours. The clinical evolution of these patients was assessed after three days by a clinical research associate through a telephone interview. Comparisons between symptoms evolution related to the pharmaceutical advice were conducted with Chi-squared tests or analyses of variance.

Results: Of 573 patients from 133 pharmacies were included in the study. Allopathic treatment alone was dispensed to 428 patients (74.7%), homeopathy treatment (alone or combined) to 145 patients (25.3%) constituting two groups. The most frequently allopathic medicine dispensed was paracetamol and for homeopathic medicine

Oscillococcinum. At inclusion, patients receiving homeopathic treatment are younger than those receiving only allopathic treatment. They notified more pronounced symptoms such as more frequent chills (53.1% vs. 31.8%, $p < 0.0001$), body aches/muscle pain (49.0% vs. 35.3% $p < 0.01$), fatigue (54.5% vs. 41.4%, $p < 0.01$), hoarseness (31.0% vs. 21.7% $p < 0.05$), sneezing (38.6% vs. 26.4% $p < 0.01$) and fever (40.7% vs. 32.0%, $p = 0.0569$). Nevertheless after three days of follow-up, both groups presented a comparable clinical improvement.

Conclusions: This study highlights the position of homeopathic treatment in the pharmacist's advice provided to patients with flu like symptoms and ENT disorders. After three days of follow-up, the clinical improvement of patients is comparable in both groups.

1023. Persistence and Appropriateness of COPD Drug Treatment in a Real-world Setting: The OUTPUL Study

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Background: Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the world. Regular treatment with long-acting bronchodilators needs to be maintained in order to control symptoms. No clinical guidelines recommend the use of inhaled corticosteroids (ICS) alone. Limited information on real-world treatment patterns exists.

Objectives: To describe patterns of drug utilization among COPD patients, to measure treatment discontinuity and assess its predictors.

Methods: A cohort of patients resident in the Lazio region and discharged from hospital with diagnosis of COPD in 2006–2007 was enrolled and observed in a two-years follow-up period. Follow-up was segmented in 6 months time-windows, in order to dynamically evaluate prescriptions of long-acting beta-agonists (LABA), tiotropium and ICS. Patients were classified into the following mutually exclusive groups: never treated, late start of treatment, discontinued, regularly treated. Discontinuation was defined as any interruption of treatment for at least 6 months. Multivariate logistic regression was performed to analyze predictors of treatment discontinuity.

Results: About 8,000 patients were included in the study, 55% were males, the mean age (SD) was 74 (10) years. More than 16% of patients did not use any long-acting bronchodilators or ICS through the entire follow-up period and about 7% began treatment more than 6 months after the COPD hospital discharge. Moreover, 31% of patients discontinued treatment during the 2 years following hospitalization. About 3,700 patients (46%) have been regularly treated with the study drugs but, among these, more than 1,000 patients used ICS alone for at least 6 months. Predictors of long-acting bronchodilators discontinuity were: female gender, psychiatric illness, cerebrovascular disease, obesity, heart failure, chronic nephropathy and area of residence.

Conclusions: In clinical practice, the COPD pharmacotherapy is definitely inconsistent with clinical guidelines. Appropriate recognition of factors associated with treatment discontinuation is expected to result in an improved doctor-patient relationship and in a consequent better control of disease.

1024. Abstract withdrawn by author.

1025. Targets for Interventions To Optimize Pharmacotherapy in Asthma COPD Patients

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Objectives: To provide targets for tailored interventions by identifying suboptimal pharmacotherapy in asthma and COPD patients. *Study design*: Drug-utilization study using a large prescription database.

Methods: Drug dispensing data for 2009 were retrieved from the IADB.nl database. Via different analyses possible suboptimal pharmacotherapy was depicted. Topics included frequent use of SABA, combination therapy with β-blockers, exacerbations and ICS, incidence of oral candidiasis following ICS initiation and combination therapy of LABA and ICS.

Results: Of 36% of patients identified as asthmatic did frequently use SABA. Of 29% of this group did not receive any preventive medication. About 15% of the asthmatics and 5% of the COPD patients prescribed β-blockers is prescribed non-cardio selective β-blockers. Half of the COPD patients with two or more exacerbations per year are prescribed ICS. Prescription symmetry analysis showed a sequence ratio of 2.56 (95% CI 2.01–3.27) for oral candidiasis medication following ICS initiation in chronic ICS users. Prescription of a LABA without an ICS to asthmatics is 3%. Asthma patients receiving one single inhaler containing both a LABA and an ICS is 92%.

Conclusions: The outcomes of this study offer perspectives for pharmacists and GPs to develop tailored interventions to improve pharmacotherapy in asthma and COPD patients.

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1026. Astro-Lab Project: Assessment of the Safety of Long-Acting Beta Agonists (LABAS) in Asthma by Combining Health-Care Databases and Direct Patient Follow-Up): Focus on Detailed Pattern of Use of Therapy

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Background: The efficacy of long-acting β-agonists (LABAs) in asthma has been demonstrated but their safety remains an issue, particularly in children. Although co-therapy with inhaled corticosteroids (ICs) is recommended in persistent asthma, its inadequate use may contribute to the occurrence of exacerbations. Hence, differential exposure to ICS and LABAs may be a key issue to explain poor asthma outcomes related to LABAs, in monotherapy and with concomitant ICs.

Objectives: To assess the safety of LABAs in children and adults when used alone and in combination with ICs, compared with ICs alone, with a specific interest on detailed patterns of use, and their relationship with adverse outcomes.

Methods: The current project combines state-of-the-art approaches, bringing together groups with expertise in respiratory drug safety research, observational study design, and patient adherence behaviour. An innovative approach is proposed, which triangulates, over 2 years of follow-up, prescription and clinical data from general-practice databases; delivery data from claims databases, and data directly obtained by computer-assisted telephone interviews from study participants about their characteristics, understanding of disease and therapy, and treatment use. Of 1,500 Children (6–12 years) and 1,500 adults (13–40 years) with persistent asthma, at risk of adverse outcomes, will be included, in France and in the United Kingdom.

Results: The observed patterns of use of LABAs and ICs will be ranked according to the risks of adverse outcomes. The role of potential differences in patterns of use between ICS and LABAs will be investigated. The project will also move beyond the state-of-the-art in adherence research by incorporating provider-level factors as possible determinants of adherence behaviours.

Conclusions: These data will be of interest to the scientific community, patients' associations, physician's associations, and regulators with respect to recommendations to prescribers.

1027. Drug Utilization Patterns for Routine Therapies in Patients with Cystic Fibrosis

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Background: Drug utilization studies about routine therapies (RT) in patients with cystic fibrosis (CF) are scarce.

Objectives: This study characterizes the changes in RT and explores associations between RT utilization and selected patient characteristics.

Methods: We utilized Medicaid data of 26 US states linked to the National CF Registry from 1999 to 2006 to establish a cohort of CF patients (0–18 years). We required patients to have at least 6 months continuous Medicaid eligibility and at least 1 encounter in the CF registry in each study year. Annual prevalence for RT was determined as the proportion of patients with a continuous 30-day drug supply in each study year; estimates were stratified by disease severity and age. Calculated prevalence ratios were adjusted using the Serfling method.

Results: Although mean age increased from 9.6 (95% Confidence Interval [CI]: 9.3–9.8) in 1999 to 12.4 years (CI: 12.1–12.7) in 2006, there was no change in mean forced expiratory volume (FEV1) (83.3%; CI: 81.9–84.7% vs. 82.6%; CI: 81.4–83.7) and body-mass-index (BMI) (63.2%; CI: 60.5–65.9% vs. 64.6%; CI: 61.9–67.3); we observed an increase in the mean weight-for-length (WFL) in 0–2 year olds (56.3%; CI: 51.4–61.2 % vs. 66.5%; 95% CI: 60.9–72.1). We observed for the following RTs at least a 15% increase in prevalence ($p > 0.05$): oral macrolide antibiotics (MA) (5.2–32.9%), leukotriene antagonists (LA) (5.7–23.6%), inhaled corticosteroids (ICS) (16.2–47.7%) and dornase alfa (DA) (44.3–65.4%). Subtle increases were observed for inhaled bronchodilators (IBS) (60.8–74.0%), inhaled tobramycin (25.9–33.7%), oral corticosteroids (OCS) (3.3–4.9%) and pancreatic enzymes (85.5–85.8%). Use of the following RTs decreased: mast cell stabilizers (21.8–4.1%), mucolytics (5.1–3.5%), oral ibuprofen (4.1–3.1%) and oral bronchodilators (1.0–0.3%). Stratified analyses suggested an increased use of RTs with age and disease severity except for ICS, LA and OCS.

Conclusions: During our study period we observed a more aggressive introduction of routine therapies, especially MA, DA, ICS, and LA. Future studies assessing efficacy and safety of these multi-drug regimens may be necessary.

1028. Dosing Frequency and Adherence to Inhaled Corticosteroids in Patients with Asthma

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Background: Non-adherence to prescription medications is common and is associated with poor outcomes. Simplifying dosing regimens for some chronic disease conditions may result in better adherence; however, little is known as to the effect of dosing on adherence to asthma maintenance therapy.

Objectives: To determine whether once-a-day dosing is associated with higher adherence to inhaled corticosteroids (ICS) when compared with more-than-once-a-day dosing among patients with asthma.

Methods: We used claims data from a large healthcare system to identify patients aged 12–56 years with asthma seen between January 1, 2006 and December 31, 2010. The cohort was limited to patients with no prior diagnosis of congestive heart failure or chronic obstructive pulmonary disease, those not on ICS/long-acting beta-agonist (LABA) combination therapy, and persons with ≥2 prescription fills for an ICS. Patient follow-up continued from the initial ICS fill until one of the following: the last ICS fill in the observation period, a switch of ICS dosing regimen, or the initiation of ICS/LABA combination therapy. Medication fill events were linked with prescription information to estimate total days supplied. Adherence was estimated by calculating a continuous multiple-interval measure of medication availability. Analysis of covariance was used to describe the relationship between adherence in patients treated with once-a-day verses more-than-once-a-day ICS therapy.

Results: Among the 244 patients who met the inclusion criteria, 36% were African American and 65% were female. Twenty-six individuals were on a once-a-day regimen and 218 were on a more-than-once-a-day regimen. Adherence was higher among those prescribed ICS once-a-day as compared with more-than-once-a-day ICS therapy (62.6% vs. 40.5%, respectively; $p = 0.001$). This significant difference persisted after adjusting for age, sex, race, asthma severity, and use of additional asthma controller therapy.

Conclusions: A once-a-day dosing regimen was associated with higher adherence to ICS therapy. Clinicians should consider simplifying asthma treatment regimens, especially if this can be achieved without changing the effective dose that patients receive.

1029. Prediction of Non-Invasive Ventilation, Mechanical Ventilation and Mortality among Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Danish Population-Based Cohort Study

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Background: Hospitalization for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a serious event that may require non-invasive ventilation (NIV) and mechanical ventilation (MV). The estimated 90-day case fatality rate after AECOPD hospitalization is 14%. However, data on predictors of AECOPD outcomes are limited.

Objectives: To develop separate models to predict the probability of (1) receiving NIV; (2) receiving MV; and (3) dying within 30 days of hospitalization with an AECOPD event.

Methods: We included all COPD patients living in Northern Denmark with at least one hospital admission with AECOPD in 2005–2010. We assessed outcomes within 30 days after day of first AECOPD admission in the study period. We developed prediction models based on a list of potential predictors using backward selection methods in logistic regression models. We assessed the performance of the models with a bootstrapping approach.

Results: The model for NIV had a c statistic of 0.60 and included older age; male gender; preadmission prescriptions for antibiotics, NSAIDs/COX2 inhibitors, diuretics, statins, and bronchodilators; and preadmission history of lung cancer and connective tissue disease. The model for MV had a c statistic of 0.62 and included older age, preadmission prescriptions for antibiotics and systemic steroids, and preadmission history of venous thromboembolism. The final model for death had a c statistic of 0.69 and included older age; preadmission prescriptions for antibiotics, NSAIDs/COX2 inhibitors, diuretics, and statins; preadmission history of myocardial infarction, diabetes, asthma, lung cancer, and other tumors; prior oxygen treatment; and the number of days hospitalized during the year before AECOPD. Dichotomized predictions from this model, choosing a cut-point to balance the sensitivity and specificity, yielded a positive predictive value of 72.4% and a negative predictive value of 57.5%.

Conclusions: Although our models were not perfect, they may potentially be used for severity adjustment in registry-based studies.

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1030. The Risk of Developing Depression in Association with Previously Diagnosed Influenza Infection

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Background: Previous evidence suggests that systemic infections, particularly severe episodes, may exert neuronal damage and thereby increase the risk of developing depression. It is unknown whether influenza infections may alter the risk of depression.

Objectives: The aim of the study was to explore the association between previously diagnosed influenza infections and the risk of developing depression.

Methods: We conducted a case–control study using the UK-based General Practice Research Database (GPRD). We identified cases aged ≤80 years with an incident diagnosis of depression between 2000 and 2009 and matched them to one control patient on age, sex, general practice, calendar time, and years of history in the database. We conducted conditional logistic regression analyses to explore the association between number and timing of previous influenza infections and calculated odds ratios (ORs) with 95% confidence intervals (CIs) of developing depression, adjusted for potential confounders.

Results: We identified 72,969 case patients with an incident depression diagnosis during the study period and the same number of matched controls. As compared to patients without recorded influenza, the OR of developing depression for patients with 1, 2 or 3+ previously recorded influenza infections were 1.30 (95% CI 1.26–1.37), 1.53 (95% CI 1.34–1.75) and 1.85 (95% CI 1.37–2.50). The OR for patients with an infection recorded within 1 month prior to the onset of depression was 2.71 (95% CI 1.79–4.09).

Conclusions: In this large study population, previous influenza infections were associated with an increased risk of an incident depression diagnosis.

1031. Use of Long-Acting β-Agonists in Asthma in Spain

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Background: Asthma is a major cause of chronic morbidity and mortality throughout the world. According to the Global Initiative for Asthma, bronchodilators (inhaled short- and long-acting β2-mimetics (LABA), anticholinergics, and inhaled corticosteroids (ICS) are used to treat asthma. It is known that LABA is not recommended as a first line treatment for asthma, and it should not be given alone, but rather together with ICS. In 2010, the Regulatory Authorities reviewed the recommendations for the use of LABA. For this reason, we consider important to describe the patterns of drug use.

Objectives: To characterize the use of LABA given as monotherapy, combined therapy or LABA plus ICS, in asthma patients.

Methods: The study was conducted within the BIFAP database, a computerized Spanish GP Database. The study ran from 2002 to 2008. We identified a cohort of patients with asthma and at least one LABA prescription, being LABA plus ICS or LABA. Prevalence of LABA use was stratified by age and sex, and the concomitant use of LABA and ICS, the duration of treatment of LABA alone or combined were also studied.

Results: In a cohort of 9,622 asthma patients with at least one prescription of LABA, 8,996 (93.5%) were users of LABA combined therapy while 626 (6.5%) were users of LABA only. Use of LABA increased with age, for both sexes, being considerably higher the use of LABA combined. In those LABA alone, approximately 50% received a prescription of ICS within the same day (263 patients) or the same month (52 patients), and in children 0–12 years was higher up to 80%. In addition, only 19% (119 patients) have never received a prescription of ICS, but half had a COPD diagnosis. The treatment duration of LABA alone was up to 30 days for 256 patients (40%), and increased with age for both sexes. Finally, 1,311 (15%) of the patients were new users, while 2,511 (27%) were patients already being treated with LABA.

Conclusions: The use of LABA combined with ICS is the usual pattern of asthma treatment, and not LABA alone. The duration of treatment is often short, probably related to a typical asthma pattern. However, these findings change with an increasing age, probably due to COPD and/ or greater difficulty in treating elderly patients.

1032. Increased Risk of Mortality in COPD Patients Using Tiotropium Respimat vs. Tiotropium Handihaler

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Background: Tiotropium is a long-acting, once daily inhaled anticholinergic drug for the treatment of COPD that can be delivered either via Handihaler (dry powder inhaler) or via Respimat (soft mist inhaler). Data from

RCTs suggest that use of tiotropium Respimat is associated with an increased risk of mortality.

Objectives: To explore the risk of mortality in a cohort of either tiotropium Handihaler or tiotropium Respimat.

Methods: Within the IPCI database, a Dutch GP database, we first defined a source population of patients 40 years or older with at least 1 year of follow-up. The study period ran from 2008 to 2011. All patients were followed from start of the study untill the patient died or end of follow-up. Exact date of death and cause of death were verified for all patients. From the source population, we defined a cohort of tiotropium users (Handihaler and/or Respimat) and created episodes of use. To assess the risk of dying, we considered a 30-day carry-over effect. The risk of mortality, within these episodes of drug use, was calculated using a Cox proportional hazard regression analysis. Crude and adjusted HRs were calculated with corresponding 95% CI.

Results: From the source population, we defined a tiotropium cohort of 11,287 users providing 24.540 episodes of use. Four hundred ninety-six patients died while being exposed to either Handihaler or Respimat. Use of Respimat was associated with an increased risk of dying (HR_{crude} 1.52, 95% CI 1.24–1.87) and this association remained upon adjustment (HR_{adj} 1.33, 95% 1.07–1.65). No dose response relationship could be observed. The association was strongest for incident users and cardiovascular or cerebrovascular death, but due to low numbers not longer statistically significant (HR_{adj} 1.87, 95% CI 0.74–4.73).

Conclusions: Use of tiotropium Respimat vs. tiotropium Handihaler is associated with a 30% increased risk of mortality. So far, it is unclear whether this is a causal association or whether this can be explained by remaining confounding by COPD severity.

1033. Endothelin Receptor Antagonists and Hepatotoxicity: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background: Following the manufacturer withdrew of Thelin (sitaxentan), an Endothelin receptor antagonist (ERA), from the worldwide market due cases of fatal liver injury, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) regarding hepatotoxicity in patients treated with ERA.

Objectives: To evaluate and quantify by meta-analysis techniques the risk of hepatotoxicity associated to ERA-bosentan, sitaxentan and ambrisentan

Methods: We searched PubMed/MEDLINE, the Cochrane Library as well as regulatory agencies websites and publicly available registries of the manufacturers (before July 2011). RCTs using bosentan or sitaxentan/sitaxsentan or ambrisentan in at least one treatment group were included. Prior to data extraction, definitions of hepatotoxicity were established. Effect sizes with 95% confidence intervals (95% CI) were calculated using random effects (Dersimonian and Laird) models. Heterogeneity was analysed using Cochran's Q and I^2 tests. Egger's method was used to assess publication bias and a funnel plot was also generated.

Results: Twenty-one trials met the inclusion criteria (3,645 patients). Bosentan was the evaluated drug in 1,690 (74.2%) patients who received ERAs. Relative risk (RR) for any hepatic adverse reaction was 2.92 (95% CI: 1.85–4.62). When hepatotoxicity was defined as elevations of liver alanine or aspartate aminotransferases ≥three times the upper limit of normal, RR was 2.98 (1.69–5.25). There was a moderate, nonsignificant degree of heterogeneity between trials (I^2 = 30.5%; p = 0.09 and I^2 = 40.8%, p = 0.06). The Egger's method was non-significant (p = 0.68) but the funnel plot was skewed slightly towards higher effect values.

Conclusions: Our preliminary results suggest an increased risk of hepatotoxicity in patients receiving ERAs. Given the limited data available for ERAs other than bosentan, it is not possible to draw firm conclusions about the risk associated for the remaining drugs separately within the ERAs.

1034. Acute Renal Failure Following Oral Sodium Phosphate Bowel Preparation: A Population Based Case-Crossover Study

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Background: Oral sodium phosphate (OSP) is an effective bowel purgative and requires a substantially lower volume than polyethylene glycol-based preparative agents. Recent reports have cited an increased risk of acute renal failure (ARF) in OSP users, but there have been still debatable.

Objectives: To evaluate the association between OSP and ARF in patients without pre-existing renal diseases and aged 50 or older who were screened by colonoscopy.

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Methods: We conducted a population-based case-crossover study using the Korean Health Insurance Review and Assessment Service (HIRA) claims data from 1 January 2005 to 31 December 2009. The study population consisted of patients > 50 years of age who underwent colonoscopies after an OSP prescription prior to their first hospitalization for ARF (ICD-10 code: N17). We excluded those hospitalized patients with pre-existing renal diseases (N17-19) during the preceding 6 months. For each patient, one case and four control periods were matched. OSP use in a 1-, 2-, 4-, or 8-week window period prior to the index date was compared with OSP use in 4 earlier 1-, 2-, 4-, or 8-week control window periods. Conditional logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for concomitant medications that could induce ARF.

Results: The total number of study patients was 1,617 (54% male). The adjusted ORs when applying the 1-, 2-, 4-, and 8-week window periods were 2.0 (95% CI, 1.47–2.78), 2.2 (95% CI, 1.74–2.86), 2.6 (95% CI, 2.11–3.11) and 2.9 (95% CI, 2.49–3.78), respectively.

Conclusions: The use of OSP increases the risk of ARF in patients without pre-existing renal disease. Considering for increased frequency of colonoscopy, it should be desirable to assure renal function monitoring before and after colonoscopy.

1035. DH Vigilance Programme Against Virility Products

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Background: Virility products sold as health supplements are sometimes found with undeclared western medicines and resulting in adverse events after consumption. The Department of Health (DH) adopts a risk-based approach and operates a vigilance programme against virility products. DH collects intelligence from overseas health authorities, purchases samples from the market and the Internet for analysis and investigates adverse event reports received from healthcare professionals and the public. A territory-wide campaign against the use of virility products from dubious sources was developed with social marketing approach. DH conducts source tracing, prosecutes the sellers of these products and issues press statements. For products manufactured outside Hong Kong, DH informs the concerned health authorities.

Objectives: To review the effectiveness of DH vigilance programme against virility products found with undeclared western medicines through evaluation of the programme structure, process and outcome.

Methods: Between 2009 and 2011, reports of suspected poisoning cases related to the use of virility products and laboratory records of virility products found with western medicines are reviewed.

Results: The DH has maintained effective communication with public hospitals to collect information related to suspected poisoning cases. Review of cases showed that intelligence from overseas health authority, local drug company and the public provided essential information for DH investigation. All cases with local sources of the incriminated products identified were prosecuted. Over 50% of the cases resulted in conviction of the offenders. Both the number of suspected poisoning related to use of virility products and the number of virility products found with undeclared western medicines indicated a decreasing trend.

Conclusions: The vigilance programme against virility products by DH is effective in protecting the health of public.

1036. Androgenic Events Reported during Treatment with Intrinsa® (Testosterone Patch) Therapy: Results from an Observational Cohort Study in England

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Background: Intrinsa® (testosterone patch) is indicated for hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised women receiving concomitant oestrogen. A Prescription-Event Monitoring (PEM) study was conducted to monitor safety (particularly androgenic events) and utilisation in general practice in England. The aim was to collect a minimum of 2000 patients.

Objectives: To characterise androgenic events reported and evaluate their reversibility.

Methods: An observational cohort post-marketing surveillance study. Exposure data collected from dispensed prescriptions issued April 2007–August 2010. Outcome data (indication, event, patient demographic and selected clinical characteristics) from questionnaires sent to general practitioners ≥6 months after 1st prescription. Summary descriptive statistics were calculated. Follow up questionnaires sent for androgenic events (e.g., hirsutism, alopecia, cliteromegaly), requesting further event details, whether event resolved and if so, date/time to resolution. Time to resolution calculated as time between onset date and resolution date.

Results: Final cohort = 3019 female patients; median age 50 years (IQR: 44–55), median observation period 305 days (IQR: 258–409). Sixty-six patients (2.2%) had androgenic events reported; most frequent = hirsutism (n = 31) and hair loss (n = 16). Follow up questionnaires were sent for 66 androgenic events in 58 patients. Fifteen events (22.7% androgenic events) were reported to have resolved, whilst for 17 events (25.8% androgenic events) this was unknown. For all other events it was

unspecified if the event had resolved. Time to resolution was reported for 5 patients; median 122 days (IQR: 28–357).

Conclusions: These results provide an estimate of the frequency of androgenic events reported during Intrinsa® therapy, with the level of reversibility of these events. Overall, the frequency of androgenic events was low in the cohort and similar to the frequency reported in the SmPC, though a firm conclusion on the reversibility of these events was not possible. Nevertheless, these results contribute to the ongoing post-marketing safety assessment.

1037. 5-alpha Reductase Inhibitors and Prostate Cancer Incidence and Mortality among Men with Benign Prostatic Hyperplasia

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Background: 5-alpha reductase inhibitors (5ARI, finasteride and dutasteride) may be protective against prostate cancer, but there is concern that promising results from end-of-trial biopsies may not apply to clinical disease, and that the drug class may be associated with a reduction in low-grade disease, but an increased risk of high-grade prostate cancer.

Objectives: To quantify the incidence of prostate cancer, and time to death from prostate cancer among men with diagnosed benign prostatic hyperplasia (BPH), comparing BPH treatment groups (5ARI vs. alpha-blockers vs. no treatment).

Methods: We carried out a cohort study including all men with a diagnosis of BPH in the UK General Practice Research Database (GPRD). We classified all time at risk from BPH diagnosis as never exposed, exposed to alpha-blockers only, and ever exposed to a 5ARI. Prostate cancer incidence was calculated for each treatment category and we compared treatments adjusting for age, time since BPH diagnosis, and calendar year in a Poisson regression model. We then used linked mortality data to compare time to prostate cancer death, censoring deaths from other causes.

Results: In a feasibility analysis within a 9% subset of GPRD, we identified 7848 patients with a new diagnosis of BPH. Six hundred and sixty had a diagnosis of prostate cancer during follow-up. Of 227,835 (50%), 164,934 (36%), and 62,966 (14%) person-years were spent never treated, exposed to alpha-blockers only, and ever exposed to a 5ARI. Prostate cancer incidences were 17.6, 11.9 and 9.8 cases per 1,000 person years in the three groups respectively (adjusted IRR compared with never-treated = 0.72, 95% CI 0.61–0.86 for alpha-blockers, and 0.66, 0.50–0.86 for 5ARI, $p < 0.001$; adjusted IRR for ever 5ARI vs. alpha blocker only = 0.91, 0.68–1.21). Results for the full database, adjusted for a wide range of potential confounders, and including an analysis of prostate cancer-specific mortality, will be presented.

Conclusions: Our results will inform the debate surrounding the suitability of 5ARIs as chemopreventive agents for men at risk of prostate cancer.

1038. Hormone Replacement Therapy and the Risk of Developing Gout

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Background: Estrogens have been reported to have a uricosuric effect which may explain to some degree the late onset of an increased gout risk for women. Hormone replacement therapy (HRT) increases the plasma volume and has been shown to slightly decrease the uric acid level.

Objectives: We aimed at studying the association between use of HRT and the risk of developing incident gout.

Methods: We conducted a case–control study using the UK-based General Practice Research Database (GPRD). We identified female cases aged between 18 and 80 years with an incident gout diagnosis between 1995 and 2009 and matched them to one control women on age, general practice, calendar time, and years of history in the database. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of developing gout in relation to previous use of HRT. We stratified by timing of use and by number of prescriptions, and additionally adjusted for potential confounders.

Results: The study encompassed 23,707 cases with a first-time gout diagnosis and the same number of matched controls. As compared to non-users, current users of 1–9, 10–19, or 20+ prescriptions of HRT showed a tendency towards an increased OR of developing gout of 1.28 (95% CI 1.07–1.54), 1.09 (95% CI 0.91–1.31), and 1.32 (95% CI 1.14–1.52), respectively. Past use of HRT was not associated with an altered risk of developing gout. Further analyses regarding administration route (oral vs. transdermal) or product composition (opposed vs. unopposed) are currently under work and results will be presented at the conference.

Conclusions: This analysis suggests that patients who currently use HRT are at a slightly increased risk of developing gout, whereas past users are not. Use of HRT does not seem to materially alter the risk of a gout diagnosis in postmenopausal women.

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1039. HRT Use amongst Women in India and Adverse Events Associated with It: A 4 Months Study from a Large Indian Hospital

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Background: HRT is one of the treatments offered by physicians for physical and psychological ailments of menopausal women with either very low or non-existent estrogen levels; a process that happens either because of natural or surgical menopause. HRT replaces decreasing oestrogen and can often provide relief for many symptoms. HRT is not commonly prescribed in India because of the expense and the other is a mindset.

Objectives: To determine the extent of HRT that is prescribed to urban women in India and also to determine the extent of adverse events associated with its use.

Methods: The study was conducted in one of the large hospital in India from October 2011 to January 2012. Women between the ages of 45 and 65 year who attended the menopause clinic and were prescribed HRT was identified and medical records scrutinized to determine adverse events associated with its use.

Results: A total of 585 women were prescribed HRT for various indications. Most common HRT and the indication for prescribing was – Osteoporosis (164; 28%; Estrogen 0.625 mg); menopausal symptoms (147; 25.1%; Tibolone 2.5 mg); atrophic vaginitis/urethritis (143; 24.5%; Estrogen 0.625 mg); climacteric vasomotor symptoms (74; 12.6%; Estrogen 0.625 mg) and amenorrhea (57; 9.7%; Progesterone 400 mg). Most common adverse events reported in women prescribed HRT were – weight gain; headache; Dizziness, GI disturbance, Skin irritation, Musculoskeletal pain, Breast tenderness enlargement, depression. The rare adverse events reported were hepatic impairment (10; 1.8%) and altered glucose tolerance and lipids (18; 3.1%). Approximately 30% (176 women) prescribed HRT discontinued treatment due to adverse events.

Conclusions: Our study has shown that HRT is not commonly prescribed in India. Short-term HRT has a higher acceptance and compliance from Indian women than long term therapy. Common reasons for refusal were reoccurrence of vaginal bleeding and a feeling that menopause was a natural occurrence and needed no treatment. Lack of awareness was also a reason for low usage, however, women can also be deterred with increased adverse events (30%) that can lead to discontinuation.

1040. Drug Use and Risk of Nephrotic Syndrome: A Danish Population-Based Case–Control Study

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Background: Drugs may cause nephrotic syndrome (NS). We therefore undertook a population-based case–control study to examine the risk with use of selected drugs.

Objectives: To examine the odds ratio for NS in patients receiving a prescription for antibiotics, non-steroidal anti-inflamatory drugs (NSAIDs), penicillamine, captopril, tamoxifen, lithium or gold.

Methods: We performed this population-based case–control study in three Danish counties including 1.4 million people. We identified all patients with a NS diagnosis between 2000 and 2010 through Danish National Patient Registry (DNPR) and identified 10 controls matched on index date (corresponding to admission date for NS in cases), age and sex. We used a virtually complete outpatient prescription database to identify filled prescription for gold, antibiotics, NSAIDs, penicillamine, captopril, tamoxifen and lithium within 1 year before NS or the corresponding index date in controls. We also included hospital codes for tamoxifen use. We computed the Charlson comorbidity Index score (excluding moderate to severe renal diseases) in a 5 years period before index date to adjust for comorbidity in three levels (score of 0, 1–2, or 3+). We computed unadjusted and comorbidity-adjusted odds ratios (ORs) using conditional logistic regression.

Results: We identified 605 cases with a diagnosis of NS and 6,050 controls. In the year before index date, 80.5% of cases and 74.4% of controls used antibiotics, 53.2% of cases and 45.3% of controls used NSAIDs, 0.2% of cases and 0.1% of controls penicillamine, 1.5% vs. 0.5% used captopril, 0% vs. 0.05% used tamoxifen, and 0.5% vs. 0.3% used lithium. No cases or controls used gold. The adjusted ORs for NS was 1.35 (95% CI 1.08–1.68) for antibiotics, 1.49 (95% CI 1.22–1.83) for NSAIDs, 1.13 (0.13–9.83) for penicillamine, 1.88 (0.85–4.17) for captopril, and 1.44 (0.40–5.11) for lithium.

Conclusions: Use of drugs, including antibiotics and NSAIDs, was associated with increased risk of nephrotic syndrome.

1041. Effect of the Listing of Cinacalcet in the Quebec Drug Formulary on Parathyroidectomy Rates

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Background: Despite availability of phosphate binders, active vitamin D analogues and more recently calcimimetics, parathyroidectomy (PTX) remains indicated for cases of severe secondary hyperthyroidism, a common and serious disease among patients with chronic kidney disease.

Objectives: The aim of this study was to investigate PTX rates trend between 2001 and 2010, and to evaluate if recent availability of cinacalcet, a calcimimetic, modified that trend.

Methods: Using the provincial administrative database, we conducted a retrospective study of adult patients receiving chronic dialysis treatments between 2001 and 2010. Both incident and prevalent patients were included. We excluded patients with < 90 days of follow-up, a prior PTX or a kidney transplant. A PTX was the primary outcome and was identified through hospital discharge summary procedure codes and RAMQ physician claim codes. Since cinacalcet became available progressively from September 2004 (Health Canada approval) to June 2006 (provincial reimbursement), we used different cut-off dates in that period: September 2004, January 2005, June 2005, January 2006, and June 2006. Bimonthly PTX rates were calculated throughout the study duration. We modeled the effect of cinacalcet availability on PTX rates using an ARIMA intervention model.

Results: We followed 12,795 chronic dialysis patients (mean age 64 years, 39% female, 82% hemodialysis) for a mean follow-up of 3.3 years. We identified 267 PTX during follow-up, translating to an average rate of 7.0 per 1,000 person-years (p-y). The average PTX rate before cinacalcet availability was 11.4/1,000 p-y, and became 3.6/1,000 p-y after cinacalcet formulary listing. Only January 2006 as an intervention date in the ARIMA model was associated with a change in PTX rates (estimate: -5.58, $p = 0.03$). Other intervention dates were not associated with statistically significant lower PTX rates.

Conclusions: We found decreased rates of PTX after January 2006, corresponding to cinacalcet availability. However, decreased rates may be due to other factors occurring simultaneously with cinacalcet introduction and further studies are needed to confirm these findings.

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