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Safety and use of medicines in mental health at the psychiatric hospital of the Republic of Tatarstan (Russia)

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Abstract. Neuroleptics' safety and use survey was conducted with the aim to develop a drug use monitoring system at a regional psychiatric hospital as an efficient tool of improving use of anti-psychotics. 7080 Side-effects report slips included into the regular medical charts for the period of 4 years (2000–2003) and 385 medical charts for the twelve months of the year 1960 were studied. The total daily neuroleptic load was calculated with the help of Chlorpromazine equivalents and ATC/DDD methodology. It was confirmed that clinical form of paranoid schizophrenia, age and gender contribute to the increased susceptibility of patients to development of movement disorders: women, patients over 60 years of age and youngsters, and patients with cerebral-organic deficiency being the most vulnerable. The most common patterns of inadequate prescribing practice included needless overuse of neuroleptics; combination treatment of highly dosed neuroleptics; simultaneous prescribing of anticholinergics (trihexyphenidyl) with neuroleptics; clozapine use only as a sedative component. Pharmacovigilance system proved to be an effective instrument in monitoring but not necessarily improving prescribing practices.

1. Background/Introduction

Improving use of psychotropics is one of the priority public health issues. Through the last decades neuroleptic prescriptions increased steadily [8]. Since their first introduction in early fifties of the 20th century psychotropic medicines (chlorpromazine) fundamentally changed the situation in psychiatric institutions. Antipsychotics (or neuroleptics) allowed to control the symptoms of schizophrenia, and if prescribed adequately and timely favorably affected prognosis preventing irreversible personality changes of schizophrenic patients. However severe side-effects, including development of disabling movement disorders resulted in poor compliance of patients and stimulated development and introduction into practice of new generations of antipsychotics. Both this factors contributed to the emerging problem of poor prescribing of neuroleptics to schizophrenic patients.

We attempted to develop pharmacovigilance module for rational/quality use of psychotropics in treating schizophrenic patients at a regional psychiatric hospital – the Clinical Psychiatric Hospital of the

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Ministry of Health of the Republic of Tatarstan. This is the first Russian study on the safety of neuroleptics and consumption of psychotropics at a regional hospital.

The Republic of Tatarstan is an administrative region of the Russian Federation situated on the Volga river with population of 3 760 892 (2003 year). The prevalence of psychiatric and behavioural disorders in the year 2000 was 2346 per 100 000 population and in the year 2003 – 2446 per 100 000 population, being higher in men and in the cities as compared to women and rural population. The incidence of these mental health disorders in the year 2000 was 215 per 100 000 population and in the year 2003 – 243 per 100 000 population.

The Clinical Psychiatric Hospital of the Ministry of Health of the Republic of Tatarstan is a closed specialized institution with 2100 beds, 56 departments, including somatic, infectious diseases, tuberculosis, pediatric and psychosomatic disorders departments. It comprises specially constructed system of buildings with more than 135-years of history. The number of patient bed days a year was around 700 000 for the last five years.

The objective of the study was to develop pharmacovigilance monitoring system in a psychiatric hospital as an efficient tool of improving use of anti-psychotics.

2. Methods

Side-effects report slips and regular medical charts of the schizophrenic patients of the Clinical Psychiatric hospital of the Republic of Tatarstan were used for the analysis. 7080 side-effects report slips included into the regular medical charts for the period of 4 years (2000–2003) and 385 medical charts for the twelve months of the year 1960 were studied. The year 1960 was used as historic control since at that time the only available neuroleptic was chlorpromazine. Movement disorders described by physicians in the report slips were grouped by the severity of presentation according to Abnormal Involuntary Movement Scale (AIMS) [9] and classification of Avrutsky (1974) [2]. Reactions were estimated as mild at less than 8 points of AIMS scale, as moderate – at 8 to 24 points of AIMS scale and as severe – at 24–32 points of AIMS scale.

The total daily neuroleptic load was calculated with the help of Chlorpromazine equivalents [3,4] and used for the analysis of interrelation between the neuroleptic load and the severity of movement disorders. The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) methodology [1,7] was used for the dosage analysis of neuroleptics in paranoid schizophrenia. Analysis of neuroleptic induced side effects was carried out by age, gender, length of neuroleptic treatment and forms of paranoid schizophrenia.

2.1. Statistics

Differences between mean values of doses in groups with normally distributed variables were assessed using Student's paired t-test. To evaluate normality of variances Kolmogorov–Smirnov and Shapiro–Wilk normality tests were used and homogeneity of variances was estimated using Levene and Brown–Forsythe tests. Differences between variables that were not normally distributed were evaluated by Wilcoxon–Mann–Whitney test. A probability of less than or equal to 0.05 was considered significant.

The statistical analyses were performed using SPSS software (USA), version 11.0. Data are presented as mean $\pm$ SD.

3. Results

In the year 1960 at the Clinical Republican Psychiatric hospital the only neuroleptic used was chlorpromazine and its mean prescribed daily dose was 0.97 ± 0.12 DDD ($n = 385$). Physicians in the medical charts described only mild movement disorders.

In the years 2000–2003 in 98% of all the studied cases neuroleptics were used in combination therapy including at least two neuroleptics. The total daily neuroleptic load causing movement disorders of various degrees of severity depended on the clinical form of paranoid schizophrenia, being the lowest in patients with cerebral-organic deficiency (Table 1).

The total daily doses of individual neuroleptics in terms of DDDs and oral chlorpromazine units are presented in Table 2. In the majority of cases these doses exceeded corresponding DDDs.

The doses causing acute and chronic movement disorders in men were consistently higher than those in women with statistical significance for the most frequently used neuroleptics – haloperidol, chlorpromazine and clozapine (Table 3).

Table 1

Total daily neuroleptic load causing movement disorders in patients with paranoid schizophrenia

Clinical form	Daily neuroleptic load (in oral chlorpromazine mg), M ± SD
Paranoid schizophrenia	2547 ± 107 mg
n^*/N^{**} 273/3835 → %	6–8%
Paranoid schizophrenia with cerebral-organic deficiency	1653 ± 123 mg
n/N 162/1293 → %	12–14%
Schizophrenia with hallucinative-paranoidal syndrome	3053 ± 116 mg
n/N 232/2337 → %	10–12%

$^*n$ – number of patients with movement disorders, $^{**}N$ – total number of patients (2000–2003).

Table 2

Mean daily doses of neuroleptics used in combination therapy causing acute and chronic movement disorders of various degrees of severity (in terms of DDDs and in oral chlorpromazine units, 2000–2003)

Neuroleptic	Total daily dose (M ± SD, DDDs)	Total daily neuroleptic load (in oral chlorpromazine units, M ± SD)
Haloperidol (653)	3.4 ± 0.6	3346 ± 237
Trifluoperazine (640)	1.8 ± 0.1	1857 ± 213
Zuclopenthixol (110)	1.7 ± 0.3	1642 ± 96
Flupentixol (230)	1.5 ± 0.3	1184 ± 202
Haloperidol-decanoate (25)	1.52 ± 0.3	1520 ± 141
Fluphenazine (25)	2.3 ± 0.9	2327 ± 242
Thioproperazine (100)	3.00 ± 1.2	2047 ± 105
Risperidone (5)	1.5 ± 0.4	1463 ± 95
Quetiapine (7)	1.3 ± 0.6	1035 ± 116
Chlorpromazine (459)	1.3 ± 0.3	1204 ± 105
Clozapine (560)	0.4 ± 0.03	439 ± 49
Chlorprothixene (120)	0.5 ± 0.01	535 ± 56
Thioridazine (9)	0.5 ± 0.03	404 ± 82
Levomepromazine (10)	0.4 ± 0.1	463 ± 95
Sulpiride (11)	0.2 ± 0.1	235 ± 78

Table 3

Mean daily doses of neuroleptics used in combination therapy causing acute and chronic movement disorders of various degrees of severity in men and women (in terms of DDDs, 2000–2003)

Neuroleptic	Total daily dose (M ± SD, DDD)	
	Women	Men
Haloperidol	$2.73 \pm 0.11^{*}$ ($n = 258$)	3.48 ± 0.19 ($n = 143$)
Chlorpromazine	$1.64 \pm 0.2^{*}$ ($n = 221$)	2.96 ± 0.23 ($n = 137$)
Clozapine	$0.12 \pm 0.02^{*}$ ($n = 172$)	0.54 ± 0.17 ($n = 114$)

$^{*}P < 0.05$ – difference between doses in men and women.

Table 4

Mean daily doses of neuroleptics used in combination therapy causing acute and chronic movement disorders of various degrees of severity in patients of different age groups (in terms of DDDs, 2000–2003)

Neuroleptics	Total daily dose (M ± SD, DDD)		
	under 40 years of age	40–60 years of age	over 60 years of age
Haloperidol	2.22 ± 0.5 ($n = 180$)	$2.55 \pm 0.3^{*}$ ($n = 279$)	$1.3 \pm 0.2^{*}$ ($n = 186$)
Chlorpromazine	$1.77 \pm 0.06^{*}$ ($n = 129$)	$1.95 \pm 0.15^{*}$ ($n = 197$)	$1.34 \pm 0.13^{*}$ ($n = 131$)
Trifluoperazine	$1.56 \pm 0.2^{*}$ ($n = 182$)	$2.7 \pm 0.1^{*}$ ($n = 277$)	$1.1 \pm 0.01^{*}$ ($n = 175$)
Clozapine	0.21 ± 0.01 ($n = 154$)	$0.81 \pm 0.18^{*}$ ($n = 244$)	$0.3 \pm 0.02^{*}$ ($n = 162$)

$^{*}p < 0.05$ when comparing the doses of the patients over 60 years of ages and other age groups.

In patients over 60 years of age movement disorders developed with the use of lower daily doses of haloperidol, chlorpromazine, trifluoperazine and clozapine (Table 4), thus demonstrating that vulnerability (susceptibility) to neuroleptic side effects increased with age. The mean dose for any antipsychotic causing movement disorders in schizophrenic patients over 60 years of age was 1.01 ± 0.01 DDD.

The most frequently used combinations of neuroleptics for the management of acute episode of paranoid schizophrenia are listed in the Table 5. No significant difference in effectiveness of any of the combinations was observed. The time required to achieve pharmacological control over the symptoms did not differ significantly with any of the used combinations. Monotherapy with haloperidol or risperidone was used in a less that 2% of patients. Noteworthy is the fact that clozapine was used only as a sedative component in a combination therapy. Conventional neuroleptics for the management of acute episodes of paranoid schizophrenia were less costly.

The issue of whether or not movement disorders are dose dependent is still not completely resolved. We looked at the severity of presentation of movement disorders and at the total daily neuroleptic load of patients with paranoid schizophrenia. Our findings were not fully consistent to allow assumptions of dose dependency of movement disorders (Table 6).

We compared the data on safety of neuroleptics with consumption data for the year 2003 when we introduced the ABC/VEN analysis for the first time in history of the healthcare of the region. It was confirmed that the haloperidol and chlorpromazine, responsible for the absolute majority of movement disorders, were the leaders of consumption followed by trihexyphenidyl. Consumption of the newer atypical antipsychotics – risperidone, quetiapine and olanzapine was less that 10 DDDs per 100 bed days. At the same time the costs of these three atypical neuroleptics constituted nearly one third of the annual drug budget.

Table 5
Neuroleptics' combinations commonly used for the incisive therapy (acute episode) of paranoid schizophrenia. Calculations of costs

Neuroleptics' combinations	Cost of 1 DDD (roubles)	Mean daily doses of neuroleptics in terms of DDDs (M ± SD)	Mean cost of the required course of treatment (roubles)	Total cost of treatment of acute episode (roubles)
Haloperidol	1.008	2.9 ± 0.06	36.72	95.72
Chlorpromazine	2.74	1.25 ± 0.11	35	
Clozapine	5.7	0.36 ± 0.02	24	
Risperidone	133.75	1.8 ± 0.06	3371	3400
Clozapine	5.7	0.36 ± 0.02	29	
Haloperidol	1.008	2.9 ± 0.06	32.53	74.11
Chlorpromazine	2.74	1.25 ± 0.11	31	
Trifluoperazine	0.78	1.81 ± 0.04	10.58	
Haloperidol	1.008	2.9 ± 0.06	38.27	55.91
Trifluoperazine	0.78	1.81 ± 0.04	17.64	
Haloperidol	1.008	2.9 ± 0.06	36.72	36.72
Risperidone	133.75	1.8 ± 0.06	3371	3371

Table 6
Mean daily doses of neuroleptics used in combination therapy causing acute and chronic movement disorders by degree of severity (in terms of oral chlorpromazine units, 2000–2002)

Severity of movement disorders	Mild	Moderate	Severe
Paranoid schizophrenia			
Year 2000	1700 ± 312 ($n = 32$)	1934 ± 172 ($n = 41$)	$2439 \pm 181^*$ ($n = 26$)
Year 2001	2002 ± 190 ($n = 28$)	1859 ± 390 ($n = 37$)	$1562 \pm 182^*$ ($n = 19$)
Year 2002	1368 ± 219 ($n = 19$)	1946 ± 100 ($n = 31$)	1682 ± 76 ($n = 17$)
With cerebro-organic deficiency			
Year 2000	1020 ± 84 ($n = 17$)	1134 ± 312 ($n = 25$)	–
Year 2001	$1178 \pm 212^*$ ($n = 10$)	1358 ± 212 ($n = 17$)	$2283 \pm 361^*$ ($n = 19$)
Year 2002	$498 \pm 231^*$ ($n = 17$)	1068 ± 127 ($n = 23$)	983 ± 166 ($n = 14$)
With hallucinative-paranoidal syndrome			
Year 2000	$2076 \pm 142^*$ ($n = 20$)	2673 ± 232 ($n = 28$)	3436 ± 123 ($n = 23$)
Year 2001	1834 ± 237 ($n = 17$)	2573 ± 246 ($n = 26$)	1986 ± 135 ($n = 21$)
Year 2002	$1722 \pm 98^*$ ($n = 25$)	2259 ± 218 ($n = 22$)	2984 ± 426 ($n = 19$)

$^*p < 0.05$ when comparing the total daily neuroleptic loads of the patients stratified by the degree of severity of movement disorders.

4. Discussion

The analysis of prescribing practice of psychiatrists demonstrated that it was not meeting the requirements of modern evidence-based approaches to quality psychopharmacotherapy. The most common patterns of inadequate prescribing practice included needless overuse of neuroleptics with total daily doses greatly exceeding 2–3 DDDs and combinations of highly dosed neuroleptics. This is an example of approach traditionally being justified by physicians by the fact of treatment-refractory schizophrenia, despite the persistent lack of response to treatment and exceeding recommended maximum beneficial doses [5]. Overprescribing of psychotropics was also well documented in a cross-sectional study in nursing and old-age homes in Sweden, where treatment with psychotropics was used for approximately

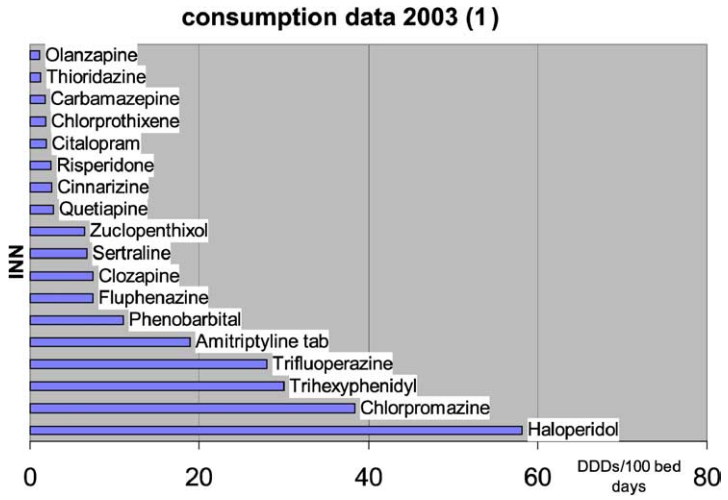

Fig. 1.

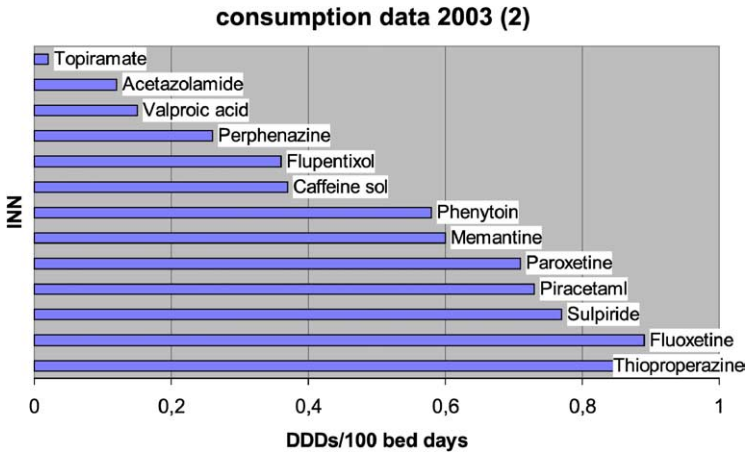

Fig. 2.

50% of elderly people without a determined psychiatric diagnosis [10]. In our study anticholinergics (trihexyphenidyl) were commonly prescribed simultaneously with neuroleptics on the commencement of therapy of patients with paranoid schizophrenia and regardless of side effects profile. Trihexyphenidyl was used in a standard dose in all patients as a prophylactic rather than treatment measure, the major reason for its withdrawal being severe tachycardia and urine retention. This problematic point in neuroleptic drug prescription was also well documented in a French national cross-sectional survey [6].

Clinically unjustified polypharmacy and combination neuroleptic treatment resulted in development of movement disorders.

The first generation atypical antipsychotic clozapine was exclusively used as a sedative component of treatment. This usage pattern might partially explain the fact that leucopenia or agranulocytosis was not observed in our setting with clozapine use. The results of side effects monitoring were regularly reported to the physicians aiming at improving their prescribing habits.

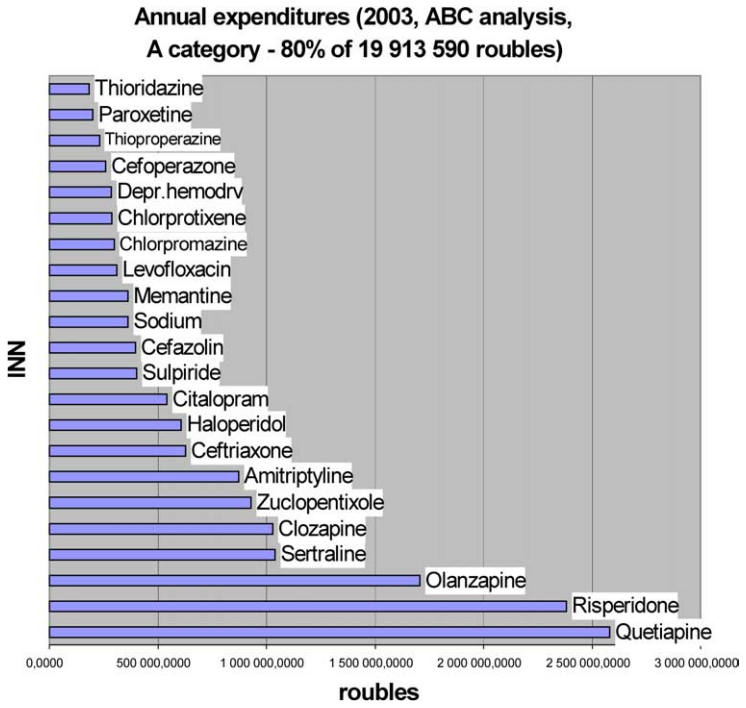

Fig. 3.

Despite these reports and regular monitoring the so-called preventive use of anticholinergics as well as polypharmacy in antipsychotics' prescription persisted during the 4-year study period. At the same time total daily neuroleptic load tended to decrease through the 4-year period as well as polypharmacy.

The results of our study prove the necessity of furthering interventions focused on psychotropics beneficial effects and safety, such as introduction of educational activities for psychiatrists and emphasizing the importance of further drug safety and drug use monitoring in this field.

5. Conclusion. Strength and limitations of the study

Neuroleptic-induced movement disorders represent the major problem in treating paranoid schizophrenia, with increased incidence as compared to the historical control of the year 1960. Clinical form of paranoid schizophrenia, age and gender contribute to the increased susceptibility of patients to development of movement disorders: women, patients over 60 years of age and youngsters, and patients with cerebral-organic deficiency being the most vulnerable.

Drug use and side effects monitoring methodology aimed at improving of pharmacotherapy of schizophrenic patients by means of side effects' registration cards in regular medical charts proved to be an effective instrument in monitoring but not necessarily improving prescribing practices.

Steps to move forward would not be only monitoring of drug use and side effects as well as education of physicians on regular basis, but also development of clinical guidelines, coordinated with the formulary list and better use of administrative and managerial resources.

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