

PRESCRIBING PATTERNS FOR INPATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS IN A PSYCHIATRIC HOSPITAL IN SLOVENIA: RESULTS OF 16-MONTH PROSPECTIVE, NON-INTERVENTIONAL CLINICAL RESEARCH

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received: 7.11.2016;

revised: 7.3.2017;

accepted: 19.4.2017

SUMMARY

Background: In Slovenia, there has been no evidence about the prescribing patterns for inpatients with psychotic disorders. The research aims to analyze drug utilization patterns for inpatients with psychotic disorder that are coded as F20-F29 according to International Classification of Diseases (ICD) 10th revision (schizophrenia spectrum disorders).

Subjects and methods: Prospective research was conducted at the Psychiatric Hospital Idrija. The medical records of the inpatients admitted over a 12-month period were collected from the beginning to the end of their hospitalization.

Results: A total of 311 inpatients with 446 hospitalizations were included, producing a total of 3954 medication prescriptions. Medications prescribed pro re nata (the use of as needed) were also taken into account. Antipsychotics (N=1149, 43% of prescriptions) were the most often prescribed medications, followed by anxiolytics, antiparkinsonians, antidepressants, mood stabilizers and cardiovascular drugs. A total of 256 (82%) inpatients received at least one pro re nata medication. It was observed that the studied population was treated with one antipsychotic on 27 percent of prescriptions.

Conclusions: Inpatients with schizophrenia spectrum disorders were exposed to a large number of different drugs. They were not received only psychotropic drugs but also other medications. With the knowledge about medications the implementation of clinical pharmacy services to the psychiatrists would significantly improve medication of inpatients with psychotic disorders and polypharmacotherapy.

Key words: inpatients – schizophrenia - prescribing patterns

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INTRODUCTION

Previously, the primary focus in treating psychotic disorders was on controlling positive symptoms with conventional, first-generation antipsychotics (FGA). These agents have poor efficacy on negative symptoms and some serious adverse reactions (Stahl 2009, Park-poor & Agius 2014). Today, psychotic disorders treatment is more complex, with more comprehensive options now aiming to provide relief in all symptom domains, improve compliance and prevent relapse, reduce adverse reactions and improve functional outcomes (Lehman et al. 2004). The increasing use of atypical, second-generation antipsychotics (SGA) reduced the mean duration of admission (Chong et al. 2010).

Patients with psychotic disorders often require long-term, highly intensive treatment and care. Individuals with schizophrenia have a 20% shorter life expectancy than the population at large and greater vulnerability to diabetes, coronary heart disease, hypertension and emphysema (Hennekens et al. 2005, Newcomer & Haupt 2006). Consequently, they are usually receiving a large number of different medications (polypharmaco-

therapy). Moreover, the lifestyles of people with psychotic disorders often associated with alcohol and street drugs use, poor dietary habits, obesity and high rates of smoking, contribute to several illnesses (Covell et al. 2006).

Some of antipsychotics have been associated with weight gain, the onset of diabetes, increases in lipid levels, changes of the electrocardiogram, prolactin elevation, cataract formation, movement disorders and sexual dysfunction (Stahl 2009). Polypharmacotherapy with antipsychotics may further increase the risk of adverse reactions (Weiden et al. 1998).

Some of the previous studies on prescribing practices in psychiatric hospitals in Europe examined only the patterns of psychotropic prescribing (Jordanova et al. 2011, Davids et al. 2006, Rittmannsberger et al. 1999, Szkultecka-Dębek et al. 2016).

In Slovenia, there has been no evidence about the prescribing patterns for psychiatric inpatients. The research is conducted to quantify all drug utilization patterns for inpatients with psychotic disorder that are coded as F20–F29 according to International Classification of Diseases (ICD) 10th revision (schizophrenia spectrum disorders / SSD).

SUBJECTS AND METHODS

Study cohort

The Psychiatric Hospital Idrija (PBI) is one of the six psychiatric hospitals (one of them is university clinic) in Slovenia. PBI carries out its activities in the area with over than 308,000 inhabitants. It is peripherally located on the West of the country and as the second largest Slovenian psychiatric hospital generally reflects the organization of inpatients mental health care in Slovenia. During the period of the research the hospital had about 170 beds for acute and long-term inpatients.

Eligible inpatients met the following inclusion criteria: psychotic disorders that are coded as F20–F29 according to International Classification of Diseases (ICD) 10th revision and aged between 18 and 65 years. The exclusion criteria were as follows: inpatients with liver and/or kidney diseases and pregnant women. Data were collected from inpatients admitted to PBI over a 12-month period (from December 1, 2009 to November 30, 2010). Inpatients were monitored from the beginning to the end of their hospitalization; the last one was discharged in March 2011, so the research period was 16 months. No patient dropped out from the study. The study has been approved by the National Medical Ethics Committee of the Republic of Slovenia.

Data collection

Documented inpatient's characteristics were sex, age, body mass index, smoking status, coffee and alcohol consumption, marital status, diagnoses and number and length of hospitalization. All medications prescribed in the ward were recorded. All data were recorded in special forms prepared for the purpose of the research.

Statistical analysis

Statistical analysis was done using the IBM SPSS statistics 20 software package (IBM SPSS, Chicago, IL, USA). Frequencies (percentages) were used to describe categorical variables and for descriptive purposes; variables were presented as arithmetic means or medians.

RESULTS

Inpatient's characteristics

A total of 311 inpatients were included in the research. The mean age was 42 years (min =19, max =65) and the mean body mass index was 27 (min =16, max =60). 69 percent of the inpatients (N=213) were smokers (76% of males vs. 58% of females), 95 percent (N=294) consumed coffee (96% of males vs. 92% of females), 53 percent consumed alcohol (72% of males

vs. 28% of females) and 77 percent of the inpatients were single (89% of males vs. 62% of females).

47 percent of the inpatients were hospitalized due to one of the types of schizophrenia. Paranoid schizophrenia (F20.0) was predominant diagnosis (N=98, 32%, 36% of males vs. 25% of females), followed by acute and transient psychotic disorders (30%). Catatonic schizophrenia and delusional disorder have not been diagnosed.

Hospitalization's characteristics

There were 446 hospitalizations. In the research period, the majority of the inpatients (73%) were hospitalized once, 17 percent twice and 10 percent three times or more (one inpatient was hospitalized seven times). 23 percent of the inpatients were hospitalized for the first time.

On average, inpatients stayed at the ward 44 days (median =34, min =1, max =286).

Medication prescriptions

A total of 3954 medication prescriptions were analyzed. Medications prescribed pro re nata (the use of as needed) are taken into account, but these drugs were analyzed separately. The most often prescribed drug was antiparkinsonian biperiden (N=231, 9%), followed by anxiolytic diazepam (N=177, 7%). According to the Anatomical Therapeutic Chemical classification index (ATC), antipsychotics were prescribed most frequently, followed by anxiolytics, antiparkinsonians, antidepressants, antiepileptics (mood stabilizers) and cardiovascular drugs (Figure 1).

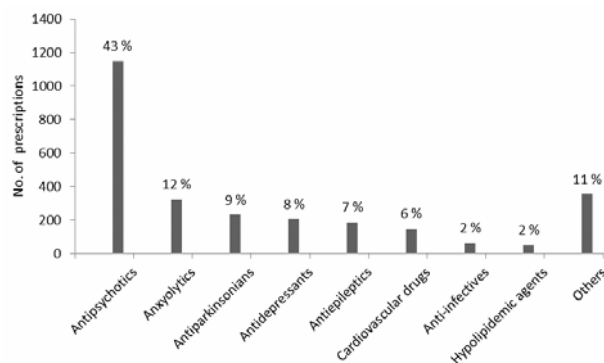


Figure 1. Summary of prescribing medications (drugs prescribed pro re nata are not taken into account)

Antipsychotics

Among antipsychotics, the most frequently prescribed were fluphenazine (N=157, 14%), olanzapine (N=155, 14%), quetiapine (N=135, 12%), haloperidol (N=131, 11%) and clozapine (N=121, 11%). Table 1 shows the prescribing daily doses (PDD) of antipsychotics. The relationship between the number of antipsychotics and the number of prescriptions is given in Table 2. The dual medications of antipsychotics are presented in Table 3.

Table 1. The prescribed daily dose of antipsychotic (PDD) and comparison of the average maintenance dose per day for a drug used for its main indication in adults (DDD)

Antipsychotic	DDD (mg)	PDD mean (SD) (mg)	PDD median (min/max) (mg)	Average length of time of antipsychotic use (min/max) (day)
Amisulpride	400	388 (244)	324 (800/100)	23 (4/210)
Aripiprazole	15	16 (6)	15 (30/5)	35 (2/204)
Clozapine	300	203 (119)	192 (600/15)	44 (3/279)
Flupenthixol	6	9 (4)	8 (18/3)	39 (6/130)
Fluphenazine	10	16 (8)	15 (39/3)	35 (2/162)
Haloperidol	8	19 (8)	17 (43/2)	31 (1/187)
Levomepromazine	300	142 (142)	100 (300/25)	21 (7/38)
Lithium	/	903 (120)	900 (1164/750)	39 (6/97)
Lithium R	/	907 (108)	900 (1286/900)	37 (3/79)
Olanzapine	10	15 (4)	15 (24/5)	35 (1/162)
Paliperidone	6	7 (2)	7 (12/3)	25 (1/82)
Promazine	300	175 (122)	150 (419/25)	38 (2/204)
Quetiapine	400	286 (223)	217 (800/25)	23 (2/133)
Quetiapine SR	400	352 (206)	318 (800/50)	30 (2/106)
Risperidone	5	4 (2)	4 (7/1)	30 (2/186)
Sulpiride	800	182 (121)	100 (371/100)	15 (3/33)
Ziprasidone	80	132 (31)	136 (160/71)	44 (8/94)
Zuclophenthixol	30	26 (12)	20 (51/13)	35 (9/72)

DDD – maintenance dose per day for a drug used for its main indication in adults; PDD – prescribed daily dose of antipsychotic; R – controlled release; SD – standard deviation; SR – slow (extended)-release

Table 3. Dual medications of antipsychotics

Antipsychotic	Amisulpride	Aripiprazole	Clozapine	Flupenthixol	Fluphenazine	Haloperidol	Levomepromazine	Lithium	Lithium R	Olanzapine	Paliperidone	Promazine	Quetiapine	Quetiapine SR	Risperidone	Sulpiride	Ziprasidone	Zuclophenthixol
Amisulpride	/	6	41	0	32	18	0	0	0	4	0	0	0	0	3	1	1	0
Aripiprazole	6	/	91	30	9	23	0	0	21	28	6	0	36	33	38	0	0	3
Clozapine	41	91	/	27	441	227	0	49	31	46	16	7	23	26	74	2	72	17
Flupenthixol	0	30	27	/	2	1	0	0	3	4	0	3	0	5	0	6	3	0
Fluphenazine	32	9	441	2	/	45	6	25	13	201	1	54	85	112	57	5	86	0
Haloperidol	18	23	227	1	45	/	3	35	30	338	19	63	67	83	20	0	7	12
Levomepromazine	0	0	0	0	6	3	/	0	0	0	0	3	4	0	0	0	0	3
Lithium	0	0	49	0	25	35	0	/	4	0	0	5	6	29	13	0	18	0
Lithium R	0	21	31	3	13	30	0	4	/	33	0	3	13	34	27	0	15	0
Olanzapine	4	28	46	4	201	338	0	0	33	/	30	18	14	14	55	0	3	11
Paliperidone	0	6	16	0	1	19	0	0	0	30	/	7	13	1	21	1	0	0
Promazine	0	0	7	3	54	63	3	5	3	18	7	/	15	7	6	1	0	1
Quetiapine	0	36	23	0	85	67	4	6	13	14	13	15	/	21	24	0	0	0
Quetiapine SR	0	33	26	5	112	83	0	29	34	14	1	7	21	/	51	1	0	13
Risperidone	3	38	74	0	57	20	0	13	27	55	21	6	24	51	/	0	0	0
Sulpiride	1	0	2	6	5	0	0	0	0	0	1	1	0	1	0	/	0	0
Ziprasidone	1	0	72	3	86	7	0	18	15	3	0	0	0	0	0	0	/	0
Zuclophenthixol	0	3	17	0	0	12	3	0	0	11	0	1	0	13	0	0	0	/

R – controlled release; SR – slow (extended)-release; Shaded – avoid combination; *italic* – the most frequent combinations

Table 2. Number of antipsychotics in prescriptions

No. of antipsychotics	No. of prescriptions	Percentage of prescriptions
0	28	<1
1	1066	27
2	1847	47
3	876	22
4	128	3
5	8	<0.2
6	1	<0.1
Total	3954	100

Anxiolytics

Among 322 prescriptions of anxiolytics for regular use (not pro re nata), diazepam (N=177, 55%), lorazepam (N=94, 29%) and alprazolam (N=46, 14%) were the most often prescribed.

Antiparkinsonians

Only two antiparkinsonians were prescribed: biperiden and pramipexole. Biperiden showed a high number of prescriptions (N=231) and pramipexole had only one prescription.

Antidepressants

Sertraline, mirtazapine and escitalopram were the most frequently prescribed antidepressants (Table 4).

Table 4. Summary of prescribing antidepressants

Antidepressants	No. of prescriptions	Percentage
Sertraline	65	32
Mirtazapine	28	14
Escitalopram	23	11
Venlafaxine	18	9
Paroxetine	14	7
Fluoxetine	13	6
Duloxetine	12	6
Citalopram	8	4
Bupropion	8	4
Clomipramine	5	2
Tianeptine	5	2
Agomelatin	4	2
Amitriptyline	1	0.5
Maprotiline	1	0.5
Total	205	100

Antiepileptics (mood stabilizers)

Among antiepileptics, valproic acid (N=110, 60%), lamotrigine (N=45, 24%) and carbamazepine (N=16, 9%) were the most frequently prescribed.

Medications prescribed pro re nata

We take into account only medications that have been prescribed pro re nata and also administered. A total of 256 (82%) inpatients received medications prescribed pro re nata. 22 percent (N=55) of them received two medications, 16 percent (N=42) of them received one medication but some inpatients constantly received a greater number of different medications prescribed pro re nata. The most frequently drugs prescribed pro re nata were anxiolytics (N=161, 63%), hypnotics (N=152, 59%), analgesics (N=113, 44%), antipsychotics (N=109, 43%), laxatives (N=91, 36%) and antiparkinsonians (N=61, 24%).

DISCUSSION

The crucial differences between previous research on the pharmacological medication of psychiatric inpatients and our research are as follows: the previous research examined only the patterns of psychotropic prescribing for inpatients with different psychiatric disorders, our research examined the prescribing patterns of all medications for inpatients with specific disorders coded as F20–F29, some of the previous research were carried out on the certain day and they were retrospective, our 16-month research was prospective, observational and non-interventional (Jordanova et al. 2011, Rittmannsberger et al. 1999). A limitation of this research is its monocentric character, nevertheless the number of included inpatients (N=311) was high enough to get representative data, especially for Slovenia.

In the observed population, the portion of males was higher than that of females (58% vs. 42%). Inpatients were smokers, singles, had BMI in the overweight range and the majority of them consumed coffee and alcohol, respectively (Covell et al. 2006). In the research period, due to the frequent relapse of SSD, almost one third of the inpatients (27%) were hospitalized several times.

Use of medications

Our inpatients were exposed to a polypharmacotherapy. A considerable amount of prescribed medications was an anticholinergic antiparkinsonian biperiden as its role is to mitigate the adverse reactions (extrapyramidal symptoms) of FGA (Sweetman 2007). Concomitant use of two or more anticholinergic drugs may increase the risks associated with anticholinergic activity. Such effects may include, dry mouth, dry eyes, blurred vision, urinary retention, constipation and cognitive impairment (Stockley 2002).

We found 322 (12%) prescriptions of anxiolytics, mostly diazepam, lorazepam and alprazolam, prescribed for regular use. 63 percent of medications prescribed pro re nata were benzodiazepines. In the Australian research of use pro re nata medications in acute inpatients found that the second highest rate of prescription of regular medications were benzodiazepines (23%), with

diazepam accounting for 18% of the total prescribed regular prescriptions (Stein-Parbury et al. 2008). In psychiatric hospitals in Eastern Europe (Albania, Croatia, Romania and Serbia) was also very high prevalence of use of benzodiazepines (Jordanova et al. 2011). Anxiolytics (benzodiazepines) are used for the treatment of anxiety and its related symptoms such as emotional, neurotic and sleep disorders. Although these drugs were prescribed pro re nata inpatients used them regularly for more than two weeks, which constitutes a considerable risk of tolerance and dependence, accompanied with withdrawal and rebound syndromes (Stahl 2009, O'Brien 2005).

In combination with antipsychotics, antidepressants were often used to treat negative psychotic symptoms. A total of 205 prescriptions of antidepressants were recorded (Table 4). Some combinations of antipsychotics and antidepressants should be avoided. For example, the concomitant use of highest risk QTc-prolonging antidepressants (e.g., citalopram, escitalopram, fluoxetine) with any other QTc-prolonging agent (e.g., flupentixol, paliperidone, quetiapine, sulpiride, ziprasidone, zuclopentixol) should be avoided. Many such combinations are listed contraindications for these drugs. Concomitant use is expected to substantially increase the risk for serious toxicities, including the development of torsades de pointes (TdP) or other significant ventricular tachyarrhythmias. Patients with other risk factors present (e.g., older age, female sex, bradycardia, hypokalemia, hypomagnesemia, heart disease and higher drug concentrations) would be at an even higher risk for these potentially life-threatening toxicities (Drew et al. 2010).

The inpatients were also given non-psychotropic medications (21% of the total prescribed regular prescriptions): cardiovascular drugs, hypolipidemic drugs, anti-infectives and others (Figure 1) (Stahl 2009, Newcomer & Haupt 2006, Hennekens et al. 2005). The use of some medications is probably justified since they reduce or eliminate adverse reactions of antipsychotics (Covell et al. 2006, De Hert et al. 2006).

It was anticipated that antipsychotics would be the most frequently used drugs for inpatients with SSD (Figure 1).

Guidelines of the World Federation of Societies of Biological Psychiatry give priority to SGA over FGA (Hasan et al. 2012). The reasons for a relatively high percentage (41%) of prescribed FGA (flupentixol, fluphenazine, haloperidol, levomepromazine, promazine, sulpiride and zuclopentixol) lie in the fact that they represent a traditional, low-priced alternative to SGA (amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone), they are available in different dosage forms and, finally, they exhibit effective sedation in restless and often aggressive inpatients (Stahl 2009, Parkpoor & Agius 2014). Almost at the same time, even 60 percent of the inpatients with psychosis in Eastern Europe received FGA (Jordanova et al. 2011).

82 percent of the acute and long-term inpatients received medications prescribed pro re nata. In the Australian research, 97 percent of acute inpatients received medications prescribed pro re nata (Stein-Parbury et al. 2008). There is a high risk of polypharmacotherapy and drug interactions, especially when pro re nata medications are different than those regularly prescribed. It was found that in a large number of the inpatients (N=109, 35%) antipsychotics in different dosage forms were prescribed pro re nata: a) intramuscular injections – haloperidol (N=35, 14%), aripiprazole (N=4, 2%) and zuclopentixol (N=1, 0.5%), b) tablets – olanzapine (N=27, 11%), haloperidol (N=18, 7%), clozapine (N=17, 7%), risperidone (N=13, 5%), fluphenazine (N=7, 3%), promazine (N=7, 3%) and quetiapine (N=7, 3%) and c) solution – haloperidol (N=38, 15%). In the Australian research, the second most frequently administered pro re nata medications (18%) were FGA (Stein-Parbury et al. 2008).

Amisulpride, clozapine, levomepromazine, promazine, quetiapine, risperidone, sulpiride and zuclopentixol were prescribed in too low doses (Table 1). The differences between the average maintenance dose per day for a drug used for its main indication in adults (DDD) and the mean prescribed daily dose (PDD) are in some cases substantial (Table 1). These observations imply that dosing of antipsychotics is not optimal. The same conclusions have been drawn in an Italian district (Bolcato et al. 2014). Comparing PDD at the first introduction of antipsychotic (data are not presented) with DDD we found that antipsychotic therapy was started with smaller doses which was followed by larger doses on the basis of titration (the differences between min PDD and max PDD are very large for the majority of antipsychotics). Based on the number of hospitalizations, olanzapine (N=149), fluphenazine (N=148), quetiapine (N=132), haloperidol (N=122), clozapine (N=115) and risperidone (N=109) were the most frequently prescribed antipsychotics. The duration of therapy with antipsychotics oscillates from only few days to the defined number of months, with clozapine which is used at the farthest (Table 1).

Crucial information (Table 2) was also the number of prescribed antipsychotics per inpatient. It was observed that studied population was treated with one antipsychotic on 27 percent of prescriptions. Two and three antipsychotics were concomitantly prescribed on 47 percent and 22 percent of prescription, respectively. It was found that more than three antipsychotics were prescribed concomitantly on 4 percent of prescription. This is again not in agreement with recommendations of the British Association for Psychopharmacology where it is clearly stated that combinations of antipsychotics should be avoided except in the case of switching (Barnes 2011). During the observational period, at least one switch of antipsychotic was recorded in 37 percent of the inpatients (abrupt switch was recorded in 31 percent). In specific cases, it is possible that multiple

antipsychotics were used concurrently during the switching process. It was also observed that in less than 1 percent of prescriptions (N=28) antipsychotics were not prescribed. These cases may confirm the statement of some authors claiming that a non-pharmacological approach may be suitable for some specific groups of patients with schizophrenia (Matei et al. 2014). In Austrian psychiatric clinics, it was observed that more than half the schizophrenic inpatients are prescribed more than one antipsychotic and from 1 to 12 percent antipsychotics were not prescribed (Rittmannsberger et al. 1999).

Table 3 shows all dual medications of antipsychotics that may not be appropriate as they represent a potential risk of interaction (Canales et al. 2001) and also Guidelines of the World Federation of Societies of Biological Psychiatry recommend the use of only one antipsychotic (Hasan et al. 2012). Some combinations of antipsychotic should be avoided, for example, the concomitant use of amisulpride with other antipsychotics (Table 3). The most common prescribed combinations of antipsychotics were clozapine/fluphenazine (N=441, 11%), haloperidol/olanzapine (N=338, 9%), haloperidol/clozapine (N=227, 6%), olanzapine/fluphenazine (N=201, 5%) and quetiapine/fluphenazine (N=197, 5%).

Dual medications of long acting with short acting antipsychotics were most often prescribed for a limited period where switching antipsychotics was indicated: fluphenazine decanoate/fluphenazine (N=280, 7%), fluphenazine decanoate/clozapine (N=163, 4%), fluphenazine decanoate/quetiapine (N=121, 3%), flupenthixol decanoate/clozapine (N=120, 3%) and haloperidol decanoate/haloperidol (N=113, 3%). Dual medications of long acting flupenthixol decanoate with clozapine should be avoided (Drew et al. 2010).

Among the long acting antipsychotics three combinations were prescribed concomitantly: flupenthixol decanoate and fluphenazine decanoate were prescribed together twice. This is an unacceptable result as it is assumed that two long acting antipsychotics should not be prescribed concomitantly (Stahl 2009).

During the research period, we did not interfere with the psychiatrist's decisions. Although the national guidelines for the treatment of patients with schizophrenia are now quite old (Kocmur et al. 2000), psychiatrists use also other international guidelines, including the very recent ones. In general, the authors assume that prescribing practices, described in this research, do not depart significantly from current treatment guidelines for patients with schizophrenia. However, there are still several possible improvements. One of them is the use of recommended daily doses of antipsychotics in cases where prescribed doses were too low. The once quite frequent practice of prescribing very large doses of antipsychotic medications, well over the recommended dosing ranges, is nowadays very rare, probably also due to Mental Health Act which limits the use of doses above recommended range. Psychiatrists are expected to

be knowledgeable of psychotropic drug interactions, but we recorded a lot of combinations of medications (also psychotropic) which should be avoided. With the knowledge about drug (interactions, adverse reactions, dosage, modes of admission) the implementation of clinical pharmacy services to the psychiatrists would significantly improve medication of inpatients with psychotic disorders and polypharmacotherapy.

CONCLUSIONS

For the first time in Slovenia, we provided a detailed overview of the prescribing patterns for inpatients with SSD. It was concluded that the medication in PBI is not optimal for at least few reasons. First, inpatients were exposed to a large number of different drugs. Second, there was a high risk for clinically relevant drug interactions because of polypharmacotherapy, especially with psychotropic drugs. Finally, the majority of inpatients received more than one antipsychotic at the same time and nine out of sixteen antipsychotics were prescribed in too low doses.

The results of the research indicated that additional measures are needed to improve medication. The inclusion of a clinical pharmacist in the process of drug treatment is one of the most efficient solutions. Positive outcomes such as significant improvement in clinical response and drug-induced extrapyramidal symptoms together with high satisfaction with the clinical pharmacy services are well documented (Canales et al. 2001). Moreover, a well-designed prospective research will have to be conducted as the key to successful improvement of drug therapy in psychiatric inpatient.

Psychiatrists and specialist in internal medicine at the PBI are now able to consult on the use of medications by a clinical pharmacist. This is particularly important for inpatients with polypharmacotherapy also with psychotropics, comorbidity, liver and/or kidney diseases, pregnant women and elderly.

Acknowledgements:

The authors would like to express their thanks to the management of PBI for all the support in conducting the research.

Conflict of interest: None to declare.

Contribution of individual authors:

Cvetka Bačar Bole: design of the study, literature searcher and analyses and interpretation of data;

Mitja Pišlar: statistical analyses;

Aleš Mrhar and Rok Tavčar: design of the study, literature searchers and analyses and interpretation of data.

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