

Switching antipsychotics: Results of 16-month non-interventional, prospective, observational clinical research of inpatients with schizophrenia spectrum disorders

CVETKA BAČAR BOLE¹
MITJA PIŠLAR²
METKA ŠEN³
ROK TAVČAR⁴
ALEŠ MRHAR^{2*}

¹ *Psychiatric Hospital Idrija, Slovenia*

² *Faculty of Pharmacy, University of Ljubljana, Slovenia*

³ *Pharmacy Kromberk, Nova Gorica Slovenia*

⁴ *University Psychiatric Hospital Ljubljana Ljubljana, Slovenia*

The study aims to identify prescribing and switching patterns of antipsychotics in clinical practice. A 16-month, prospective study was conducted at the Psychiatric Hospital Idrija, Slovenia. Inpatients ($N = 311$) with schizophrenia spectrum disorders were observed. The causes for switching antipsychotics and switching strategies were analyzed. Analyzing a total of 3954 prescriptions, the collected data confirmed that treatment strategies in this psychiatric hospital are very complex. It was found that 37 percent of inpatients had at least one switch. Moreover, switches that included three or more antipsychotics were detected. The most common causes for switching antipsychotics were adverse reactions and inefficacy or lack of efficacy. Among switching options, abrupt switch was recorded several times. As some patients are receiving several antipsychotics at the same time, it is possible that unusual switching occurs in clinical practice. It seems that the choice of switching strategy is also affected by the cause and urgency for switching an antipsychotic.

Keywords: schizophrenia, switching antipsychotics, causes, strategies

Accepted August 20, 2016
Published online September 5, 2016

Schizophrenia, schizotypal and delusional disorder are mental illnesses that affect not only the patient, but also the patient's family, friends and surroundings. Despite the fact that antipsychotics allow a better quality of life for patients, many of them never remit and may even fail to eliminate the symptoms of the disease (1). Use of antipsychotics carries risks for the patients (2). The consequence is that it becomes necessary to switch antipsychotics in order to achieve better treatment outcomes in patients with schizophrenia and provide them with greater safety (1, 3).

The benefits of switching must be balanced against the risk of the new antipsychotic, because the new one may cause other adverse reactions, it may be inefficient or incompa-

* *Correspondence; e-mail: ales.mrhar@ffa.uni-lj.si

tible with the medications the patient is already receiving, or even worsen his/her psychophysical status (3–6). Causes for switching antipsychotics may differ: adverse reactions (7–12), inefficacy or lack of efficacy (despite patient compliance in the treatment and in spite of the optimal dose of the selected antipsychotic) (13–15), drug non-compliance (due to a large number of medications, complex dosing, and negative experiences in the treatment) (16), drug-drug interactions (due to polypharmacotherapy) (17, 18), and some other causes, for example, at the request of the patient (19). As we know, several theoretical tapering options of antipsychotics are available (5, 16, 19, 20). In contrast, we do not have enough empirical data or clinical research on the antipsychotic switching strategy (20, 21). Data are sparse and contradictory, so there is no uniform position about which option of switching antipsychotics is the best (21). Moreover, most of previous clinical research was focused on switching an individual antipsychotic and was sponsored by pharmaceutical companies (21–24).

This research is conducted to examine independently the process of switching antipsychotics in psychiatric hospital practice. We endeavored to find the causes for switching, analyze the effect of various factors on switching, find out the switching strategies, determine the duration of switching, and compare the research findings with recommendations for switching antipsychotics. To our knowledge, this is the first research on this topic in Slovenia.

EXPERIMENTAL

Research design and population

Data were collected in a prospective, observational, non-interventional study of inpatients with schizophrenia, schizotypal and delusional disorder, aged 18 to 65 years, who were admitted to the Psychiatric Hospital Idrija, Slovenia, from December 1, 2009 to November 30, 2010. The exclusion criteria were as follows: inpatients with liver and/or kidney diseases, pregnant women, and patients younger than 18 or older than 65 years. 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 inpatient dropped out from the study.

Data collection

All data were recorded in six special forms prepared for the purpose of the research. Demographic information included sex, age, diagnosis, body mass and height, smoking status, coffee and alcohol consumption, marital status and number and length of hospitalization. All medications prescribed in the ward were recorded. We focused on the use of antipsychotics, so we monitored their prescribed doses, modes of administration, and information about switching: causes, pre-switching and post-switching doses, strategies, how many days were necessary to switch and the success of switches. The collection of adverse reactions as the cause for switching antipsychotics contains only the type of adverse reaction, which means that no scales or other exams were used to evaluate them. Values of the global assessment of functioning (GAF) score and the clinical global impression (CGI) were evaluated only when inefficacy or lack of efficacy was the cause for switching.

To compare daily doses of antipsychotics, chlorpromazine equivalent daily doses (CEDD) were used (25). Discovered switching strategies with antipsychotics were compared with eight available switching options: abrupt switch, ascending switch, descending switch, cross-titration, plateau switch, ascending plateau switch, descending plateau switch and plateau cross-titration.

Data 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 AND DISCUSSION

Research population

A total of 311 inpatients with 446 hospitalizations were included in the research. Demographic parameters of the study sample, which was divided into group A (inpatients with switching antipsychotics, $N = 116$, 37 %) and group B (inpatients without switching antipsychotics, $N = 195$, 63 %), are summarized in Table I.

Most of the patients (47 %) were hospitalized due to one of the types of schizophrenia. Paranoid schizophrenia was the predominant diagnosis (32 %), followed by acute and transient psychotic disorders (30 %). Catatonic schizophrenia and induced delusional disorder, which are rare psychotic disorders, have not been diagnosed in our population.

The portion of males in the observed population was higher than that of females (58 *vs.* 42 %) but, on average, females were older than males (44 *vs.* 41 years) (Table I).

During the observational time, 73 percent of patients ($N = 227$) were hospitalized once and 23 percent ($N = 72$) were hospitalized for the first time. Moreover, due to the frequent relapse of schizophrenia, some inpatients (27 %) were hospitalized several times (one of them was hospitalized seven times). Most of the inpatients (77 %) had already been hospitalized in the past; the average time of hospitalization was 44 days (Table I).

The inpatients were divided into two groups (group A and group B) to see whether the differences in patients' characteristics were connected with the switching of antipsychotics. No significant differences were found between the two groups, pointing to the probable absence of correlation between patients' characteristics (Table I) and switching antipsychotics.

Use of medications

Inpatients were exposed to a large amount of different drugs (Table II). Analyzing a total of 2706 prescriptions (drugs prescribed *pro re nata* were not taken into account), it was found that the most often prescribed drug (among all drugs) was biperiden ($N = 231$), followed by diazepam ($N = 177$), fluphenazine ($N = 157$) and olanzapine ($N = 155$). According to the Anatomical Therapeutic Chemical (ATC) classification index, antipsychotics were

Table I. Demographic and clinical parameters

| | Group A ^a No. of patients (%) | Group B ^b No. of patients (%) | Total No. of patients (%) |
|--|---|---|----------------------------------|
| Number of patients | 116 (37) | 195 (63) | 311 (100) |
| Number of hospitalizations | 129 (29) | 317 (71) | 446 (100) |
| Average time of hospitalization (days) | 66 (min = 2, max = 286) | 35 (min = 1, max = 204) | 44 (min = 1, max = 286) |
| Mean age (years) | 41 (min = 20, max = 64) | 43 (min = 19, max = 65) | 42 (min = 19, max = 65) |
| Mean BMI (kg m ⁻²) | 26.6 (min = 15.8, max = 59.6) | 26.8 (min = 15.6, max = 46.6) | 27.4 (min = 15.6, max = 59.6) |
| Smokers | 77 (66) | 136 (70) | 213 (69) |
| Coffee consumers | 108 (93) | 186 (95) | 294 (95) |
| Alcohol consumers | 60 (52) | 105 (54) | 165 (53) |
| Married | 27 (23) | 43 (22) | 70 (23) |
| Not married | 89 (77) | 152 (78) | 241 (78) |
| m/f | 60/56 (52/48) | 119/76 (61/40) | 179/132 (58/42) |
| F20.0 | 43 (37) | 55 (28) | 98 (32) |

BMI – body mass index, m/f – male/female, F20.0 – paranoid schizophrenia

^a With switching antipsychotics.

^b Without switching antipsychotics.

prescribed most frequently, followed by anxiolytics, antiparkinsonians, antidepressants, antiepileptics (mood stabilizers) and cardiovascular drugs (Table II). Since inclusion criteria for patients were psychotic disorders coded as F20–F29, with paranoid schizophrenia as predominant diagnosis, it was anticipated that antipsychotics would be the most frequently used drugs. The second most frequently given group of drugs were anxiolytics (benzodiazepines), which are used for the treatment of anxiety and its related psychological and physical symptoms such as emotional, neurotic and sleep disorders. Although these drugs were prescribed *pro re nata*, the majority of patients used them regularly for more than two weeks, which constitutes a considerable risk of tolerance and dependence, accompanied with withdrawal and rebound syndromes (12). The patients were also given cardiovascular drugs for cardiovascular problems, and antidiabetic drugs due to the metabolic syndrome (9, 11, 12). Use of these drugs is probably justified since they reduce or eliminate adverse reactions of antipsychotics (2).

Use of antipsychotics

We analyzed the prescribed doses of antipsychotics per hospitalization and determined the average prescribed daily dose and the average number of days of taking a particular antipsychotic. To compare our results on prescribing antipsychotics with the

Table II. Summary of prescribing medications^a

| Drug ATC Class | Frequency | Percentage |
|--------------------------------------|-----------|------------|
| Antipsychotics | 1149 | 42.5 |
| Anxiolytics | 322 | 11.9 |
| Antiparkinsonians | 231 | 8.5 |
| Antidepressants | 205 | 7.6 |
| Antiepileptics (mood stabilizers) | 185 | 6.8 |
| Cardiovascular drugs | 149 | 5.5 |
| Anti-infectives | 62 | 2.3 |
| Hypolipidemic agents | 49 | 1.8 |
| Antiulcer drugs | 48 | 1.8 |
| Analgesics | 46 | 1.7 |
| Respiratory system drugs | 46 | 1.7 |
| Anti-diabetic agents (oral, insulin) | 44 | 1.6 |
| Vitamins/minerals | 37 | 1.4 |
| Laxatives | 33 | 1.2 |
| Others | 100 | 3.7 |
| Total | 2706 | 100.0 |

ATC – Anatomical Therapeutic Chemical classification index

^a Drugs that were prescribed *pro re nata* are not taken into account.

prescribing habits, Table III presents the average maintenance dose per day for a drug used for its main indication in adults (DDD) according to the ATC classification system and the prescribed daily dose per hospitalization (PDD). It was found that amisulpride, clozapine, levomepromazine, promazine, quetiapine, risperidone, sulpiride and zuclopenthixol were prescribed in too low doses (PDD < DDD) (Table III). Flupenthixol, fluphenazine, haloperidol, olanzapine and sulpiride were prescribed in too high doses (PDD > DDD) and only paliperidone and ziprasidone were prescribed at the same dose (PDD = DDD). The differences between DDD and mean PDD are in some cases substantial. Moreover, the differences between max PDD and min PDD are very large for the majority of antipsychotics. Some of them (aripiprazole, olanzapine, paliperidone, quetiapine and ziprasidone) were used in maximal recommended doses. These observations imply that dosing of antipsychotics was not optimal. The same conclusion has been drawn recently in an Italian district using the same methodological approach (27).

The most frequently prescribed antipsychotic was olanzapine ($N = 126$, 41 %). This result was expected, since the guidelines for the treatment of schizophrenia recommend second generation antipsychotics (SGA), the use of which is less risky for patients (30). Nevertheless, 35 percent ($N = 108$) of patients received haloperidol and 35 percent ($N = 107$) of patients received fluphenazine, both of which are first generation antipsychotics (FGA).

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

| Antipsychotic | No. of hospitalizations | Average number of days (min/max) | DDD (mg) | PDD mean (SD) (mg) | PDD median (min/max) (mg) |
|-----------------|-------------------------|----------------------------------|----------|--------------------|---------------------------|
| Amisulpride | 20 | 23 (4/210) | 400 | 388 (244) | 324 (800/100) |
| Aripiprazole | 48 | 35 (2/204) | 15 | 16 (6) | 15 (30/5) |
| Clozapine | 115 | 44 (3/279) | 300 | 203 (119) | 192 (600/15) |
| Flupenthixol | 8 | 39 (6/130) | 6 | 9 (4) | 8 (18/3) |
| Fluphenazine | 148 | 35 (2/162) | 10 | 16 (8) | 15 (39/3) |
| Haloperidol | 122 | 31 (1/187) | 8 | 19 (8) | 17 (43/2) |
| Levomepromazine | 3 | 21 (7/38) | 300 | 142 (142) | 100 (300/25) |
| Lithium | 8 | 39 (6/97) | – | 903 (120) | 900 (1164/750) |
| Lithium R | 13 | 37 (3/79) | – | 907 (108) | 900 (1286/900) |
| Olanzapine | 149 | 35 (1/162) | 10 | 15 (4) | 15 (24/5) |
| Paliperidone | 26 | 25 (1/82) | 6 | 7 (2) | 7 (12/3) |
| Promazine | 29 | 38 (2/204) | 300 | 175 (122) | 150 (419/25) |
| Quetiapine | 66 | 23 (2/133) | 400 | 286 (223) | 217 (800/25) |
| Quetiapine SR | 66 | 30 (2/106) | 400 | 352 (206) | 318 (800/50) |
| Risperidone | 109 | 30 (2/186) | 5 | 4 (2) | 4 (7/1) |
| Sulpiride | 5 | 15 (3/33) | 800 | 182 (121) | 100 (371/100) |
| Ziprasidone | 9 | 44 (8/94) | 80 | 132 (31) | 136 (160/71) |
| Zuclopenthixol | 7 | 35 (9/72) | 30 | 26 (12) | 20 (51/13) |

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

Although it is known that FGA cause considerable adverse events, such as extrapyramidal symptoms, compared to SGA (12), this study revealed that an antipsychotic from the FGA group was prescribed to 41 percent of patients. The reasons for such a high percentage of prescribed FGA lie in the fact that they represent a traditional and low-priced alternative to SGA, they are available in different dosage forms and, finally, they exhibit effective sedation in restless and often aggressive patients.

A minority of studied patients (27 %) were treated with one antipsychotic. Two or three antipsychotics were concomitantly prescribed in 47 and 22 percent of prescriptions, respectively. It was also observed that in 3 percent of prescriptions more than three antipsychotics were prescribed concomitantly. Out of 137 prescriptions, four antipsychotics in 128, five in 8 and six antipsychotics in 1 prescription were prescribed. This is not in agreement with the 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 (28). Guidelines of the World Federation of Societies of Biological Psychiatry recommend the use of only one antipsychotic (29).

Switching antipsychotics

At least one switch was recorded in 37 percent ($N = 116$) of patients. During the observational period, 186 switches were recorded, including 22 percent ($N = 68$) of patients who had one switch, 11 percent ($N = 34$) two switches, 4 percent ($N = 11$) three switches, 1 percent ($N = 2$) five switches and one patient seven switches of antipsychotics.

Average time of switching was 9 days, maximum time was 74 days (quetiapine), and minimum time was one day (most antipsychotics).

The prescribed daily doses (PDD) of pre-switching and post-switching antipsychotics for the most common switches are given in Table IV. Risperidone was the most frequent pre-switching antipsychotic (19 % of all switches) and olanzapine was the most frequent post-switching antipsychotic (14 % of all switches). The most frequent switches were those of risperidone to paliperidone (13 cases). Despite the fact that these two drugs have a similar pharmacological profile, paliperidone improves patient medication adherence due to simple, once daily administration (22).

Antipsychotics vary greatly in potency, which is usually expressed as differences in chlorpromazine (or neuroleptic) equivalents. In an attempt to find out if there is a connection between the daily doses of pre-switching and post-switching antipsychotics, incomplete agreement about chlorpromazine equivalents was found. This is mainly due to different methods of assessing antipsychotic chlorpromazine equivalence (manufacturers'

Table IV. Prescribed daily doses (PDD) of pre-switching and post-switching antipsychotics for the most common switches

| Pre-switching antipsychotic | PDD min (mg) | PDD max (mg) | PDD mean (mg) | switching to | Post-switching antipsychotic | PDD min (mg) | PDD max (mg) | PDD mean (mg) |
|-----------------------------|--------------|--------------|---------------|--------------|------------------------------|--------------|--------------|---------------|
| Risperidone | 2 | 6 | 4 | → | Paliperidone | 3 | 12 | 8 |
| Haloperidol | 11 | 38 | 27 | → | Fluphenazine | 8 | 30 | 23 |
| Fluphenazine | 10 | 30 | 24 | → | Haloperidol | 15 | 38 | 29 |
| Risperidone | 1 | 6 | 5 | → | Fluphenazine | 5 | 30 | 22 |
| Risperidone | 1 | 6 | 4 | → | Olanzapine | 10 | 20 | 16 |
| Olanzapine | 10 | 20 | 15 | → | Risperidone | 2 | 6 | 4 |
| Haloperidol | 30 | 45 | 33 | → | Olanzapine | 15 | 20 | 18 |
| Olanzapine | 15 | 25 | 20 | → | Clozapine | 100 | 500 | 210 |
| Risperidone | 1 | 6 | 3 | → | Aripiprazole | 10 | 30 | 20 |
| Haloperidol | 15 | 30 | 27 | → | Risperidone | 4 | 6 | 6 |
| Quetiapine | 75 | 400 | 282 | → | Clozapine | 100 | 450 | 255 |

information, clinical studies, and non-clinical/dopamine binding studies), resulting in up to a five-fold difference in equivalents (6, 25). As we expected, pre-switching and post-switching antipsychotic chlorpromazine equivalent daily doses (CEDD) showed that pre-CEDD and post-CEDD are not usually equal (Fig. 1). In 20 unusual switches, pre-CEDD and post-CEDD were not calculated. Fig. 1 shows a comparison between pre-CEDD and post-CEDD values.

In 64 percent ($N = 119$) of cases, the post-switching antipsychotic was a second generation antipsychotic (SGA): in 72 percent ($N = 86$) of cases, the pre-switching antipsychotic was SGA, and in 28 percent ($N = 33$) of cases, the pre-switching antipsychotic was a first generation antipsychotic (FGA). In 24 percent ($N = 47$) of cases, the post-switching antipsychotic was FGA: in 55 percent ($N = 26$) of cases, the pre-switching antipsychotic was SGA and in 45 percent ($N = 21$) of cases, the pre-switching antipsychotic was FGA. In 12 percent ($N = 20$) of cases, the post-switching antipsychotics were not defined (depot antipsychotics and unusual switches).

Different causes for switching antipsychotics ($N = 264$) were found (Table V). Adverse reactions of antipsychotics as the cause for switching were found in 37 percent of cases. Among them, the majority were extrapyramidal symptoms (16 %), mostly caused by haloperidol, risperidone or fluphenazine. These results were expected. Adverse reactions that followed were sedation (4 %), mostly caused by olanzapine or risperidone, and weight gain (4 %) mostly caused by olanzapine. In 24 percent of cases, inefficacy or lack of efficacy was the reason for switching: olanzapine (5 %), quetiapine (4 %) and haloperidol (3 %). In 17 percent of cases, drug non-compliance (inpatient refused medicine) was the cause for switching, and in as many as 12 percent of cases, the switch was carried out at the patient's request.

Drug-to-drug interactions can lead to serious adverse reactions, failure of therapy, increased morbidity and mortality, hospital admission, prolonged length of hospital stay and elevated costs of treatment (30, 31). Unexpectedly, such interactions as the cause for switching antipsychotics were not recorded during the study period (17, 18, 25). Antipsychotics are very often given together advantageously and uneventfully, but occasionally serious

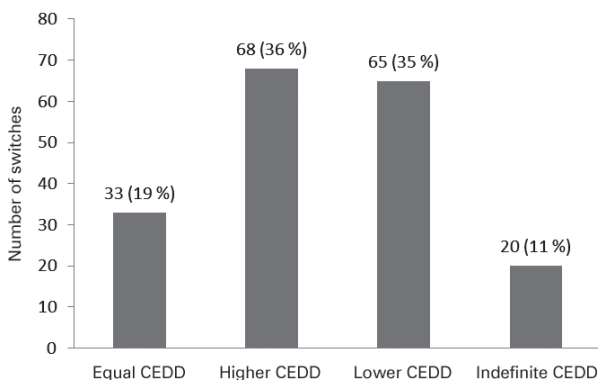


Fig. 1. Comparison of pre-switching and post-switching antipsychotic chlorpromazine equivalent daily doses (CEDD).

and even life-threatening interactions occur. These include heat-stroke under hot and humid conditions, severe constipation or adynamic ileus (18). The most common combinations of antipsychotics (analysis of a total of 2706 prescriptions) were clozapine/fluphenazine (16 %, $N = 441$), haloperidol/olanzapine (13 %, $N = 338$), haloperidol/clozapine (9 %, $N = 227$), olanzapine/fluphenazine (7 %, $N = 201$) and quetiapine/fluphenazine (7 %, $N = 197$).

Most switches (92 %, $N = 172$) included one drug replaced by another, but some unusual switches were also detected where at least three antipsychotics were involved in the switch (8 %, $N = 14$). These happened when two post-switching antipsychotics replaced one pre-switching (one by two), one post-switching antipsychotic replaced two pre-switching (two by one), one post-switching antipsychotic replaced three pre-switching (three by one) and two post-switching antipsychotics replaced two pre-switching (two by two). The reported recommendations do not mention such switches (21).

Abrupt switch was recorded in 31 percent, followed by ascending switch (23 %), cross-titration switch (17 %), a switch with at least three antipsychotics (16 %), descending switch (4 %), plateau cross-titration switch (4 %), ascending plateau switch (2 %), plateau switch (1 %), and descending plateau switch (1 %). An abrupt switch (therapeutic dose initiation of a post-switching antipsychotic and abrupt discontinuation of a pre-switching antipsychotic) was recorded several times, which was not expected because this tapering option is recommended only when amisulpride or aripiprazole are switched to paliperidone (12). An abrupt switch was most commonly used when adverse reactions of antipsychotics (11 %) or drug non-compliance (6 %) were the causes for switching. Thus it can be concluded that the choice of switching strategy is also affected by the cause and urgency for switching the antipsychotic. An ascending switch (gradual dose escalation of a post-switching antipsychotic and abrupt discontinuation of a pre-switching antipsychotic) was usually chosen when inefficacy or lack of efficacy of antipsychotics were observed (9 %) (Table V). A larger number of causes ($N = 243$) than the number of switches ($N = 186$) observed showed that for some switches more than one cause was identified. The relation between the switching strategy and the reason for switching was analyzed and the results are given in Table V.

Optimal responses to a switch were those when the patient was hospitalized for at least two weeks after switching and had no serious adverse reactions or relapse, and some positive changes (better functioning) occurred during that period. Sub-optimal responses to a switch were those when the patient was hospitalized for at least two weeks after switching and had some serious adverse reactions or relapse after switching, and when there was no benefit of switching (the level of functioning did not change). Most switches were found successful (60 %), but 9 percent of switches could not be evaluated because the patients were sent home less than two weeks after switching.

GAF and CGI

The global assessment of functioning (GAF) score was used to measure the inpatients' overall level of functioning and their ability to carry out daily activities. The clinical global impression (CGI) was used to assess the severity of the inpatient's mental illness within a specified period. Values of CGI and GAF were evaluated only when inefficacy or lack of efficacy was the cause for switching. The average value of CGI before switching was 6.1 (min = 5, max = 7), which means that inpatients were severely ill. The average value of CGI after switching was 3.5 (min = 2, max = 5), which means that some inpatients were still

Table V. Correlation between switching strategies and causes for switching

| Causes for the switching (N = 243) | Switching strategies | | | | | | | | |
|---------------------------------------|----------------------|-----------|------------|-----------------|---------|-------------------|--------------------|-------------------------|-------------------------------|
| | Abrupt | Ascending | Descending | Cross-Titration | Plateau | Ascending Plateau | Descending Plateau | Plateau Cross-Titration | At Least Three Antipsychotics |
| Unknown side effects | | | | 1 | | | | | 1 |
| Diabetes mellitus | | | 1 | | | | | | |
| Urinary incontinence | | | 1 | 1 | | | | | |
| Nausea | 1 | | | 1 | | | | | |
| Painful leg | | 1 | | | | 1 | | | |
| Insomnia | | | | | | | | 1 | |
| Anxiety | | 1 | | | | | | | |
| Sedation | 4 | 4 | 1 | 2 | | | | | |
| EPS | 10 | 9 | 2 | 6 | | 2 | 1 | 3 | 5 |
| Anticholinergic side effects | 2 | 3 | 1 | 2 | | | | | |
| Hypotension, dizziness, fatigue | 4 | 1 | | | | | | | |
| Hematologic side effects | | 1 | | | | | | | |
| Weight gain | 2 | 3 | | 4 | | | | 1 | 1 |
| Sexual dysfunction | | 1 | | | | | | | |
| Elevations in prolactin | 3 | | | 2 | | | | | |
| Inefficacy or lack of efficacy | 16 | 21 | 2 | 9 | | 1 | 1 | 4 | 5 |
| Drug noncompliance | 15 | 9 | 2 | 6 | 1 | | | 1 | 6 |
| Drug–drug interactions | | | | | | | | | |
| At the request of the patient | 9 | 6 | 2 | 5 | 1 | 1 | | 1 | 3 |
| Appropriate drug formulation | 4 | 2 | | | | | | | |
| Simpler dosing | | 1 | 1 | 1 | | | 1 | | |
| Experience of the psychiatrist | 2 | 1 | | | | | | | |
| Deliberate, from FGA to SGA | 2 | | | 1 | | | | | |
| Other | 4 | 2 | | 1 | | | | | 2 |

EPS – extrapyramidal symptoms, FGA – first generation antipsychotic(s), SGA – second generation antipsychotic(s)

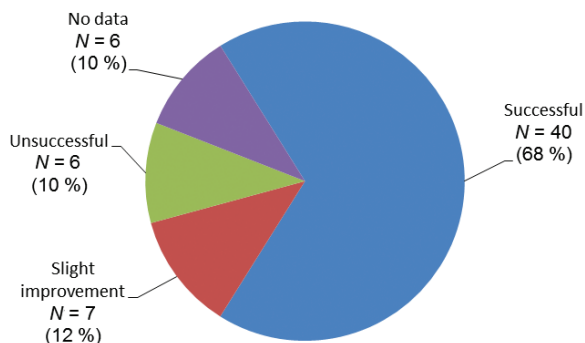


Fig. 2. Effectiveness of switching when the cause for switching was inefficacy or lack of efficacy.

mildly to moderately ill. The average difference between pre-CGI and post-CGI was 2.1 (min = 0, max = 5). The average value of GAF before switching was 25.6 (min = 5, max = 53), which means that inpatients were incapable of functioning in almost all areas. The average value of 45.2 (min = 21, max = 91) after switching indicated that some inpatients still had serious symptoms of the disease. The average difference between pre-GAF and post-GAF was 23.1 (min = 0, max = 67).

In 68 percent of switches due to inefficacy or lack of efficacy of antipsychotics, the patients' functioning and their clinical status were improved (Fig. 2). In 12 percent of switches, there were minimal changes. In 10 percent of switches, there were no changes in CGI and GAF values, whereas CGI and GAF data were missing in 10 percent of switches. This was due to either an interruption of treatment with an antipsychotic due to adverse reactions (3 cases), or the patient's discharge from the hospital in less than two weeks after switching (1 case), or drug non-compliance (2 cases).

Major limitations of our study are the lack of information about adverse reactions (no information on exams is available), the values of CGI and GAF (evaluated only when inefficacy or lack of efficacy was the cause for switching) and actual drug-drug interactions. In addition, some data were not obtained during the study period as we did not interfere with the psychiatrists' decisions (the study was prospective).

CONCLUSIONS

The research was conducted to examine independently the process of switching antipsychotics in psychiatric hospital practice in Slovenia. Moreover, for the first time, we provide a detailed overview of all drugs used for inpatients with schizophrenia spectrum disorders.

Based on the results, we can conclude that the use of antipsychotics in the Psychiatric Hospital Idrija is not optimal for at least five reasons. First, the majority of inpatients received two or more antipsychotics (73 % of prescriptions) because of too low doses of an individual antipsychotic (44 % of antipsychotics were prescribed in doses lower than DDD). Second, we detected some unusual switching of antipsychotics (8 %) where at least

three antipsychotics were included in the switch. Third, an abrupt switch was recorded several times, which was not expected because this tapering option is rarely recommended. It seems that the choice of switching strategy is also affected by the cause and urgency for switching the antipsychotic. Fourth, there is a strong potential for clinically relevant drug-drug interactions because of polypharmacotherapy, including antipsychotics, but during the study period we did not record any interactions as the cause for switching antipsychotics. Finally, some important data was not available during the study period due to incomplete medical documentation (CGI and GAF values before and after each switch, causes for switching, exams).

The presented results indicate the need for further research to eliminate some limitations of our study and to better understand some deviations in the use of antipsychotics. To conclude, once the decision is made to switch an antipsychotic, it is necessary to take an individualized switching strategy into account. We therefore suggest that clinical pharmacists should be involved in the treatment of psychiatric patients using polypharmacotherapy.

Acknowledgements. – The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 112/11/09) and has not been sponsored.

REFERENCES

1. J. M. Davis and S. Leucht, Commentary on strategies for switching antipsychotics, *BMC Med.* **6** (2008) 18–18; DOI: 10.1186/1741-7015-6-18.
2. N. H. Covell, C. T. Jackson and E. M. Weissman, Health monitoring for patients who have schizophrenia. Summary of the Mount Sinai conference recommendations, *Postgrad. Med.*, Sept. 2006, Spec. No. 20–26.
3. J. M. Kane, S. Leucht, D. Carpenter and J. P. Docherty, The expert consensus guideline series, optimizing pharmacologic treatment of psychotic disorders, introduction: methods, commentary, and summary, *J. Clin. Psychiat.* **64** (Suppl. 12) (2003) 5–19.
4. P. J. Weiden, Discontinuation and switching antipsychotic medications: understanding the CATIE schizophrenia trial, *J. Clin. Psychiat.* **68** (Suppl. 1) (2007) 12–19.
5. R. A. Rosenheck, S. Davis, N. Covell, S. Essock, M. Swartz, S. Stroup, J. McEvoy and J. Lieberman, Does switching to a new antipsychotic improve outcomes? Data from the CATIE Trial, *Schizophr. Res.* **107** (2009) 22–29; DOI: 10.1016/j.schres.2008.09.031.
6. S. Bazire, *Psychotropic Drug Directory: The Professional's Pocket Handbook and Aide Memoire*, HealthComm UK, Aberdeen 2010.
7. P. M. Haddad and A. Wieck, Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management, *Drugs* **64** (2004) 2291–2314.
8. D. D. Miller, Atypical antipsychotics: sleep, sedation and efficacy, *Prim. Care Comp. J. Clin. Psychiat.* **6** (2004) 3–7.
9. C. H. Hennekens, A. R. Hennekens, D. Hollar and D. E. Casey, Schizophrenia and increased risks of cardiovascular disease, *Am. Heart J.* **150** (2005) 1115–1121; DOI: 10.1016/j.ahj.2005.02.007.
10. M. Dossenbach, Y. Dyachkova, S. Pirildar, M. Anders, A. Khalil, A. Araszkiwicz, T. Shakhnovich, A. Akram, J. Pecenek, M. McBride and T. Treuer, Effects of atypical and typical antipsychotic treatments on sexual function in patients with schizophrenia: 12-month results from the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study, *Eur. Psychiat.* **21** (2006) 251–258; DOI: 10.1016/j.eurpsy.2005.12.005.

11. J. W. Newcomer and D. W. Haupt, The metabolic effects of antipsychotic medications, *Can. J. Psychiat.* **51** (2006) 480–491.
12. S. M. Stahl, *Stahl's Essential Psychopharmacology*, Cambridge University Press, Cambridge 2009.
13. J. A. Lieberman, T. S. Stroup, J. P. McEvoy, M. S. Swartz, R. A. Rosenheck, D. O. Perkins, R. S. Keefe, S. M. Davis, B. D. Lebowitz, J. Severe, J. K. Hsiao and clinical antipsychotic trials of intervention effectiveness (CATIE) investigators, Effectiveness of antipsychotic drugs in patients with chronic schizophrenia, *N. Engl. J. Med.* **353** (2005) 1209–1223; DOI: 10.1056/NEJMoa051688.
14. P. Chue, The relationship between patient satisfaction and treatment outcomes in schizophrenia, *J. Psychopharmacol.* **20** (Suppl. 6) (2006) 38–56; DOI: 10.1177/1359786806071246.
15. J. M. Haro and L. Salvador-Carulla, The SOHO (Schizophrenia Outpatient Health Outcome) study: implications for the treatment of schizophrenia, *CNS Drugs* **20** (2006) 293–301.
16. P. J. Weiden and M. Olfson, Cost of relapse in schizophrenia, *Schizophr. Bull.* **21** (1995) 419–429.
17. S. H. Preskorn and D. Flockhart, Guide to psychiatric drug interactions, *Prim. Psychiat.* **16** (2009) 45–74.
18. I. H. Stockley, *Stockley's Drug Interactions*, Pharmaceutical Press, London 2002.
19. A. De Nayer, E. Windhager, I. Irmansyah, I. Larmo, B. Lindenbauer, H. Rittmannsberger, T. Platz, A. Jones, J. Whiteford and C. Altman, Efficacy and tolerability of quetiapine in patients with schizophrenia switched from other antipsychotics, *Int. J. Psychiat. Clin. Pract.* **7** (2003) 59–66; DOI: 10.1080/13651500310001095.
20. P. F. Buckley and C. U. Correll, Strategies for dosing and switching antipsychotics for optimal clinical management, *J. Clin. Psychiatry* **69** (Suppl. 1) (2008) 4–17.
21. C. U. Correll, Real-life switching strategies with second-generation antipsychotics, *J. Clin. Psychiat.* **67** (2006) 160–161.
22. S. Ganesan, V. Agambaram, F. Randeree, I. Eggens, K. Huizar, D. Meuliend and on behalf of 147 investigators, Switching from other antipsychotics to once-daily extended release quetiapine fumarate in patients with schizophrenia, *Curr. Med. Res. Opin.* **24** (2008) 21–32; DOI: 10.1185/030079908X253384.
23. J. Karagianis, R. Williams, L. Davis, R. Procyshyn, N. Monga, J. Hanley, R. Chandrasena, A. Thakur and R. Dickson, Antipsychotics switching: results from a one-year prospective, observational study of patients with schizophrenia, *Curr. Med. Res. Opin.* **25** (2009) 2121–2132; DOI: 10.1185/03007990903102966.
24. H. C. Lin, M. Y. Chong, Y. Lee, W. C. Yeh and P. Y. Lin, Switching of antipsychotics to aripiprazole in the treatment of schizophrenia, *Chang Gung Med. J.* **32** (2009) 409–416.
25. D. Taylor, C. Paton and S. Kapur, *The Maudsley Prescribing Guidelines in Psychiatry*, Wiley Blackwell, Oxford 2015.
26. A. F. Lehman, J. A. Lieberman, L. B. Dixon, T. H. McGlashan, A. Miller, D. O. Perkins and J. Kreyenbuhl, American Psychiatric Association and Steering Committee on Practice Guidelines, Practice guideline for the treatment of patients with schizophrenia, *Am. J. Psychiat.* **161** (Suppl. 2) (2004) 1–56.
27. J. Bolcato, G. Terrazzani, P. Giusti, T. Walley and A. Chinellato, Atypical antipsychotic prescribing patterns in an Italian district 2001–2009 and the impact of regulatory warnings, *Open Sci. J. Clin. Med.* **2** (2014) 10–14; DOI: 10.1016/j.pnpbp.2004.06.017.
28. T. R. Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology, *J. Psychopharmacol.* **25** (2011) 567–620; DOI: 10.1177/0269881110391123.

29. A. Hassan, P. Falkai, T. Wobrock, J. Lieberman, B. Glenthøj, W. F. Gattaz, F. Thibaut, H. J. Möller and World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia, World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: Update 2012 on the acute treatment of schizophrenia and the management of treatment resistance, *World J. Biol. Psychiat.* **13** (2012) 318–378; DOI: 10.3109/15622975.2012.696143.
30. R. A. Hamilton, L. L. Briceland and M. H. Andritz, Frequency of hospitalization after exposure to known drug-drug interactions in a Medicaid population, *Pharmacotherapy* **18** (1998) 1112–1120.
31. C. S. Moura, F. A. Acurcio and N. O. Belo, Drug-drug interactions associated with length of stay and cost of hospitalization, *J. Pharm. Pharm. Sci.* **12** (2009) 266–272.
32. P. L. Canales, P. G. Dorson and M. L. Crismon, Outcomes assessment of clinical pharmacy services in a psychiatric inpatient setting, *Am. J. Health Syst. Pharm.* **58** (2001) 1309–1316; DOI: 10.3390/ijerph111010967.