ORIGINAL ARTICLES

UDC: 616.895.8-085
DOI: https://doi.org/10.2298/VSP221114007T

Retrospective analysis of hospitalization rates in patients with schizophrenia 12 months before and 12 months after the switch to once-monthly long-acting injectable paliperidone palmitate

Retrospektivna analiza stope hospitalizacija bolesnika sa shizofrenijom 12 meseci pre i 12 meseci posle uključivanja jednomesečnog dugodelujućeg injekcionog paliperidon palmitata

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Abstract

Background/Aim. There is no available published data about the use of long-acting injectable paliperidone palmitate (PP) in schizophrenia patients in the Republic of Serbia. The aim of this study was to assess hospitalization rates before and after the switch to once-monthly long-acting injectable PP in schizophrenia patients, as well as their compliance with this drug. **Methods.** We conducted a retrospective cross-sectional study in which hospitalization rates were evaluated 12 months before and 12 months after the switch to once-monthly long-acting injectable PP in 113 schizophrenia patients. The age of the enrolled patients was between 18 and 66 years. **Results.** The average age of the enrolled patients was 38.36 ± 11.62 years. Among them, 77 (68.1%) were male, and 36 (31.9%) were female. Out of the total number of 113 patients treated with once-monthly injectable PP, 78 (69.03%) were on monotherapy, while 35 (30.97%) had one additional oral antipsychotic (risperidone, olanzapine, aripiprazole, or clozapine). Out of the total number of 113 patients, 68 (60.18%) were not hospitalized in the 12-month period before the switch to once-monthly long-acting injectable PP, while 45 (39.82%) were hospitalized in the same period. Given that 8 patients out of the total number of 113 were excluded from therapy due to an adverse event or their own decision in the period after the switch to PP, the analysis of the hospitalization rate after the switch to PP was performed for the remaining 105 patients, of which 9 (8.57%) were hospitalized in the period after the switch to PP, and 96 (91.43%) were not. **Conclusion.** Our results show high compliance in the treatment with once-monthly injectable PP and a positive impact of treatment with this drug on low hospitalization rate in a 12-month period in patients with schizophrenia. Considering the availability of this drug in the Republic of Serbia, these results encourage the use of once-monthly injectable PP as an important therapeutic option in schizophrenia patients.

Key words:
antipsychotic agents; delayed-action preparations; drug-related adverse effect and adverse reactions; hospitalization; paliperidone palmitate; patient compliance; schizofrenia; serbia.

Apstrakt

Uvod/Cilj. Do sada nije bilo dostupnih publikovanih rezultata o upotrebi dugodelujućeg preparata paliperidon palmitata (PP) kod bolesnika sa shizofrenijom, lečenih u svakodnevnoj kliničkoj praksi u Republici Srbiji. Cilj rada bio je da se ispita stopa hospitalizacije bolesnika sa shizofrenijom pre i nakon uključivanja jednomesečnog dugodelujućeg injekcionog PP, kao i komplijantnost bolesnika lečenih tim lekom. **Metode.** Retrospektivnom studijom preseka ispitivana je stopa hospitalizacije kod 113 bolesnika sa dijagnozom shizofrenije, u periodu od 12 meseci pre uključivanja jednomesečnog dugodelujućeg injekcionog PP i 12 meseci nakon toga. U studiju su bili uključeni bolesnici starosti od 18 do 66 godina. **Rezultati.** Prosečna starost ispitanih bolesnika bila je 38,36 ± 11,62 godina. Među njima je 77 (68,1%) bilo muškog pola, a 36 (31,9%) ženskog pola. Od 113 bolesnika kojima je uključen PP, 78 (69,03%) bolesnika bilo je na monoterapiji, dok je 35 (30,97%) imalo dodatnu terapiju jednim oralnim antipsihotikom (risperidon, olanzapin, aripiprazol ili klozapin). Od ukupno 113 bolesnika, njih 68 (60,18%) nije bilo hospitalizovano, dok je 45 (39,82%) bolesnika bilo hospitalizovano u periodu od 12 meseci pre uključivanja jednomesečnog dugodelujućeg injekcionog PP. S obzirom na to da je od ukupno 113 bolesnika 8 isključeno sa terapije usled neželjenog događaja

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ili sopstvene odluke u periodu nakon uključivanja PP, analiza stope hospitalizacije posle uključivanja PP izvršena je u grupi od 105 bolesnika, od kojih je njih 9 (8,57%) bilo hospitalizovano u periodu posle uključivanja PP, a 96 (91,43%) nije. **Zaključak.** Naši rezultati pokazuju visoku komplijantnost bolesnika u lečenju jednomesečnim injekcionim PP i pozitivan uticaj tog leka na nisku stopu hospitalizacije bolesnika sa shizofrenijom, tokom perioda praćenja od 12 meseci. S obzirom na dostupnost PP u Republici Srbiji, ovakvi rezultati su ohrabrenje za njegovu upotrebu, kao važne terapijske opcije za lečenje bolesnika sa shizofrenijom.

Ključne reči:
antipsihotici; lekovi, produženo dejstvo; lekovi, neželjena dejstva i neželjene reakcije; hospitalizacija; paliperidon palmitat; bolesnik, saradnja; shizofrenija; srbija.

Introduction

Schizophrenia and schizophrenia spectrum disorders are chronic and debilitating disorders, frequently associated with significant and long-term negative impacts on the capability of the affected individuals to function in all aspects of living [1]. Antipsychotic medications are the backbone of treatment both for the acute phase and the maintenance treatment of these patients. Newer generation oral antipsychotic medications are recommended as the first line treatment of patients with schizophrenia both by local and international guidelines [2, 3]. Current recommendations for the long-term treatment of schizophrenia patients with antipsychotic medications are based on studies showing lower rates of relapses with continuous treatment compared to alternative strategies like discontinuation or intermittent treatment [4]. The most frequently used criteria in studies for the definition of relapse was reemergence or deterioration of disease symptoms after achieving remission and before the recovery, as well as the need for hospitalization due to psychiatric reasons. Relapse in schizophrenia has a negative impact on patient functioning and quality of life, leading to worse treatment outcomes, therapeutic resistance, prolonged periods of recovery, and decreased probability of achieving remission [5]. Besides that, relapse, including more frequent hospitalizations, significantly affects the costs of treatment for schizophrenia patients [6]. Since one of the characteristics of schizophrenia is the lack of insight, that is, the patients are unaware of their illness and its consequences, this frequently leads to challenges in long-term treatment compliance [7]. Long-acting antipsychotic medications are developed in order to improve treatment compliance and eliminate the need for every day dosing regimens [8]. Up-to-date, long-acting formulations were developed for fluphenazine, haloperidol, flupentixol, zuclopenthixol, risperidone, aripiprazole, olanzapine, and paliperidone, while long-acting formulations of fluphenazine, haloperidol, risperidone, and paliperidone are approved for use in the Republic of Serbia (RS) and reimbursed by National Health Insurance Fund [9–11].

Long-acting antipsychotic medications demonstrated plenty of advantages, like simplicity of use, following of treatment compliance, regular contact with patients, lower risk of accidental or deliberate overdose, and better correlation of dose and plasma concentration. However, some disadvantages occurred as well, like slow dose titration, longer time to establish plasma steady state, local adverse effects, or long-term adverse effects [12]. Long-acting injectable antipsychotic medications proved their efficacy by ensuring stable plasma concentrations of the drug over a few weeks period [13], decreasing the risk for treatment failure [14].

Long-acting injectable paliperidone palmitate (PP) is approved for use in the RS as a once-monthly intramuscular injection in doses of 50 mg, 75 mg, 100 mg, and 150 mg with the indication for use in adult patients with schizophrenia whose disease was stabilized with the use of risperidone or paliperidone. In some adult schizophrenia patients who previously had the response on oral paliperidone or risperidone, whose psychotic symptoms are mild or moderate, long-acting injectable PP can be used without previous stabilization with oral therapy. Besides that, PP is approved in the RS as a three-month long-acting injectable formulation in the doses of 175 mg, 263 mg, 350 mg, and 525 mg for treating adult schizophrenia patients previously stabilized with once-month long-acting injectable PP. Paliperidone exerts its pharmacological actions by binding to serotonin 5-HT2 and dopamine D2 receptors and, to a lower extent, blocks H1 histaminic and alpha-2 adrenergic receptors. Paliperidone does not bind to cholinergic receptors. The efficacy of paliperidone is demonstrated in pivotal registration studies where it showed efficacy in the acute treatment of schizophrenia, maintenance symptom control treatment, as well as in the prevention of recidivism. The safety profile of paliperidone consists of the expected adverse effects profile for the described pharmacodynamic actions – extrapyramidal syndrome, sedation/somnolence, hyperprolactinemia, increase of body weight, as well as class dependant cardiovascular adverse effects [9].

To our knowledge, there is no up-to-date published real-world evidence about the use of long-acting injectable PP in schizophrenia patients in the RS. The aim of this study was to evaluate hospitalization rates and compliance rates before and after the switch to once-monthly long-acting injectable PP in schizophrenia patients.

Methods

This is a retrospective observational cross-section study that evaluates hospitalization rates in the period of 12 months before and 12 months after the switch to once-monthly long-acting injectable PP in schizophrenia patients. This study enrolled schizophrenia patients who were administered treatment with once-monthly long-acting injectable PP in one tertiary mental health center from October 2017 to September 2019. The study was approved by the Ethics Committee of

the Clinic for Mental Disorders "Dr. Laza Lazarević", Belgrade, Serbia (No. 3096, from March 23, 2021). Retrospective data chart review and extraction were performed for the patients who met the abovementioned inclusion criteria, and the following data were collected: demographic characteristics, data about treatment duration, administered therapy, discontinuation of therapy, and data about hospitalizations. Using the method of the defined daily dose of antipsychotic medication [15], oral antipsychotic medication doses were calculated and expressed as olanzapine equivalent. The enrolled patients were 18 to 66 years old and the analysis did not include patients who did not have complete data for the follow-up period of 24 months.

Statistical analysis

Statistical analysis was performed using the statistical program SPSS (SPSS for Windows, release 24.0, SPSS, Chicago, IL). Descriptive statistics methods were used for the analysis. Numerical variables were presented as mean ± standard deviation (SD) and median with interquartile range (25^{th}–75^{th} percentile). Categorical data were presented as numbers and percentages.

Results

Sociodemographic characteristics and disease history

Considering described inclusion criteria, the study enrolled 113 patients with the diagnosis of schizophrenia who were administered treatment with once-monthly long-acting injectable PP. Regarding the demographic patient characteristics at the moment of administration of PP, it was found that the mean age of enrolled patients was 38.36 ± 11.62 years. Among them, 77 (68.18%) were male, and 36 (31.9%) were female. The median duration of overall disease treatment until the moment of administration of PP in the therapy was 72 months (range 12–348).

Treatment characterization

From the total number of 113 patients, 52 (46.0%) were switched from other long-acting antipsychotic medication (haloperidol, risperidone) to long-acting PP, while 61 (53.9%) of them were switched from oral antipsychotic medication to long-acting PP. The median dose of administered PP was 100 mg (range 75–150 mg). PP monotherapy was observed in 78 (69.03%) patients, while 35 (30.97%) had one additional oral antipsychotic (risperidone, olanzapine, aripiprazole, or clozapine). The median dose of additional oral antipsychotic medication expressed as olanzapine equivalent was 4.85 mg (range 2.81–7.38 mg).

Treatment outcomes

From the total of 113 patients who were switched to treatment with PP, 6 (5.3%) patients discontinued treatment by their own decision (without available reason for discontinuation), 2 (1.8%) discontinued treatment due to adverse effects (sedation n = 1, malignancy n = 1), and the total number of patients who continued the treatment was 105. Out of those 105 patients, 9 required hospitalization due to disease exacerbation. From the total number of 113 patients, 68 (60.2%) did not have hospitalization in the period of 12 months before the switch to once-monthly long-acting injectable PP, while 45 (39.82%) patients had hospitalization in the same period. In the analysis of the hospitalization rate after the switch to once-monthly PP, 105 patients (who were not discontinued from treatment due to an adverse event or their own decision) were included. Given that out of the total number of 113 patients, 8 were excluded from therapy due to an adverse event or their own decision in the period after the switch to PP, the analysis of the hospitalization rate after the switch to PP was performed for the remaining 105 patients, and the results showed that 9 (8.57%) of them were hospitalized in the period of 12 months after the switch, while 96 (91.43%) were not hospitalized in the same period.

Discussion

This retrospective study evaluating hospitalization rates before and after the switch to once-monthly long-acting injectable PP showed a lower percentage of hospitalizations in the same group of schizophrenia patients after the switch to PP in the follow-up period of 12 months than in the period of 12 months before the switch. Considering the limitations of this study (retrospective observational design; patients with missing data were not enrolled; heterogeneity of administered antipsychotic medication before the switch to PP; insufficient sample size for comparison regarding type, formulation, and dose of previously administered antipsychotics), no definite conclusions about the reduction of hospitalization risk in schizophrenia patients treated with once-monthly PP can be drawn based on our results. However, our results can give important insights into the treatment of schizophrenia patients with once-monthly injectable PP. The result showing that 91.43% of patients treated with once-monthly PP did not have hospitalization in the period of 12 months represents a very positive signal regarding an important outcome in schizophrenia treatment such as hospitalization, and not only the treatment outcome but also the outcome of resource utilization that hospitalization imposes. Interpretation of our results must take into consideration one important finding – 30.97% of patients had one additional oral antipsychotic medication, which prevents ascribing the result of the high percentage of patients who did not have hospitalization in the 12-month period due to the effects of PP alone. Besides that, based only on the high percentage of patients treated with PP who did not have hospitalization in the period of 12 months, we cannot draw conclusions regarding the quality of the remission, symptom severity, and functional outcomes since these parameters were not evaluated; however, the result can only be interpreted as a surrogate parameter of effectiveness.

One study [16] conducted on a larger sample (n = 2,275) of patients with schizophrenia compared hospitalization rates of patients treated with three-month injectable PP, one-

month injectable PP, long-acting injectable aripiprazole, and oral antipsychotics showed that the best rate was observed in the group of patients receiving three-month injectable PP where in the period of 12 months, 92% of patients did not have psychiatric hospitalization, while for the same period of time, the exact result for once-monthly PP was not reported, but the presented Kaplan-Meier curve showed that the value was slightly below 80%. In the same study, during the period of 18 months, 72.1% of patients with schizophrenia treated with once-monthly injectable PP were not hospitalized. Another study [17], conducted on a smaller sample (n = 51) which evaluated hospitalization rates of patients with schizophrenia treated with once-monthly PP, showed that in the period of 12 months, only 9.8% of patients had psychiatric hospitalization, which is in line with our results. The same study showed that 74% of patients during the period of 12 months, besides once-monthly injectable PP, had additional oral antipsychotic therapy, which is considerably higher than our results of 30.97%. One study showed that during the period of 12 months in 188 analyzed schizophrenia patients treated with once-monthly PP median of hospitalizations was 0 (range 0–4) [18]. While our study did not evaluate the presence, frequency, and type of adverse events of treatment with once-monthly PP, results regarding the discontinuation of treatment were very encouraging. Firstly, the result that only 6 (5.3%) out of 113 patients decided to discontinue the once-monthly PP treatment on their own (without evidence of the reason for that decision), and that only 2 (1.8%) patients discontinued due to an adverse event, can indicate good tolerability of this drug and its positive effects on treatment compliance. These results are identical to previous studies, which found low discontinuation rates for once-monthly PP [16, 18, 19].

Conclusion

Our results show high compliance in the treatment of schizophrenia patients with once-monthly injectable PP, as well as the positive impact of this drug on low hospitalization rates in these patients over the period of 12 months. Considering the availability of this drug in the RS, these results encourage its use as an important treatment option for schizophrenia patients. Further studies generating real-world evidence of once-monthly PP use should be based on larger samples from multiple centers and longer follow-up periods, make comparisons based on type, formulation, and dose of previously used antipsychotic medications, the impact of this drug on disease symptoms, functional outcomes, and lastly, but maybe most important, patient-reported outcomes.

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Received on December 14, 2022
Accepted on December 29, 2022
Online First January 2023