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Clozapine prescribing patterns in hospitalised patients in everyday clinical practice

Abstract

Aim: Clozapine is the gold standard for treatment-resistant schizophrenia. Despite clear recommendations for use, under-use and excessive delay in the use of clozapine are an ongoing findings in the literature. The aim of this study was to analyse the clozapine prescribing patterns in hospitalised patients in everyday clinical practice in Serbia. **Methods:** This cross-sectional study was conducted in Clinic for Mental Disorders "'Dr Laza Lazarević"' in Belgrade and included a sample of 238 patients, discharged from hospital treatment during 2018. Demographic, data on the clinical characteristics of the subjects, dosage and combination of clozapine with other psychopharmacs were collected retrospectively, from the patients' medical records. Descriptive and statistical hypothesis testing methods were used to analyse the primary data. **Results:** The incidence of clozapine administration was 23.5%. Clozapine was introduced into therapy after average treatment duration of 7.2 years and prior administration of three different antipsychotics. 68.1% of patients were treated with dual antipsychotic therapy prior to clozapine administration. In 53.8% of patients, clozapine was prescribed as antipsychotic monotherapy, while only eight per cent were not prescribed adjuvant therapy. The most commonly used antipsychotic in combination with clozapine was haloperidol (34.9%), while the most prescribed non-antipsychotic adjuvant drug was valproate (66%). Benzodiazepines were prescribed in 55.9% of subjects. In most subjects, the dose of clozapine was less than the standard dose. **Conclusion:** Clozapine is prescribed less frequently than expected and is often used in an irrational manner. Additional research is needed to advance its application in everyday clinical practice.

Keywords: Treatment-Resistant. Schizophrenia. Haloperidol. Valproate. Benzodiazepines.

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INTRODUCTION

Clozapine is more efficacious than all other antipsychotics; it is the only proven efficacious antipsychotic for treatment-resistant schizophrenia (TRS), has a specific anti-aggressive and anti-suicidal effect, and reduces the incidence of psychoactive substance use.[1-6] Also, clozapine administration has the effect of reducing the cost of treatment and overall mortality of patients with schizophrenia.[7-10] Regardless of its superior efficacy, due to its unfavourable side effect profile, it is a third-line drug in the treatment of schizophrenia and is used to the treatment-resistant patients.[11-14]

Serbian National Guideline for the Diagnosis and Treatment of Schizophrenia also permits the early use of clozapine in recurrently suicidal, aggressive, and patients with tardive dyskinesias.[14] Despite clear recommendations, underutilisation and delay in prescribing clozapine in everyday clinical practice are universal findings in the world literature, with the exception of China.[15-21] The most common reason for clozapine underutilisation are the fear of physicians and patients about the occurrence of serious side effects (such as agranulocytosis, myocarditis, thromboembolia, malignant cardiac arrhythmias, ileus, pancreatitis), limitations that do not allow regular monitoring of the white blood cell line, and lack of physician knowledge and experience.[22]

Data on clozapine use in Serbia are very scarce and mainly relate to the frequency of its use in limited patient samples.[23-25] The aim of this study is to analyse the prescribing patterns of clozapine in hospital treated patients in everyday clinical practice of psychiatrists in big psychiatric facility in Serbia.

MATERIAL AND METHODS

The cross-sectional study was conducted at the Clinic for Mental Disorders "Dr Laza Lazarevic" in Belgrade and included a consecutive sample of 238 patients discharged form hospital treatment during 2018, with prescribed clozapine maintenance therapy, and with diagnosis from schizophrenia spectrum disorders, in accordance with the criteria of the tenth revision of the World Health Organization's International Statistical Classification of Health and Related Problems (ICD-10).[26] The exclusion criteria were the diagnosis of primary and secondary cognitive deficits. The research was

approved by the Ethics Committee of the Clinic for Mental Disorders "Dr Laza Lazarevic" (no. 8487/1 from 16/09/2019). The data were collected retrospectively, from the patients' medical records and included: demographic data, number of previous hospitalisations, time period from beginning of treatment to clozapine administration, number of previously administered antipsychotic medications, use of antipsychotic polypharmacy (APP) prior to initiation of clozapine, presence of somatic comorbidity, use of psychoactive substances prior to hospital admission, suicidality on admission, duration of hospitalisation, and treatment prescribed on discharge. The presence of substance use was assessed on the bases of patient statements and their relatives as well as the results of qualitative urine tests and did not indicate that the criteria for substance-induced psychotic disorder were met. Suicidality was assessed as the presence of suicidal ideas, intentions, and attempts notated during the examination of the patient at admission. The analysis of treatment prescribed on hospital discharge included clozapine and adjuvant therapy. The dose of clozapine is expressed in milligrams. APP is defined as the simultaneous prescribing of at least two different antipsychotics on hospital discharge. Data on adjuvant therapy included the frequency of administration of individual antipsychotics and mood stabilisers, as well as antidepressants, benzodiazepines, hypnotics, and anticholinergics as a group of drugs. Descriptive statistical methods and methods for testing statistical hypotheses were used to analyse the primary data. Statistical differences hypotheses were tested at a significance level of 0.05. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 22.0 statistical programme (SPSS, Inc., Chicago, IL, USA).

RESULTS

In 2018, 1012 patients diagnosed with schizophrenia spectrum disorders were discharged from hospital treatment at the Clinic for Mental Disorders "Dr Laza Lazarevic", of which 238 (23.5%) were discharged with clozapine maintenance treatment. The basic demographic and clinical characteristics of the subjects are shown in Table 1. The average age of the patients was 35.5 years, most males, secondary school, unemployed, and unmarried. Just over a third of respondents (35.3%) were considered suicidal on admission, and 12.6% attempted suicide immediately before admission to the hospital. Significant somatic comorbidity (arterial hypertension, diabetes, thyroid disease, hepatitis, anaemia, chronic obstructive pulmonary disease) was present in 27.7% of patients, while a quarter consumed psychoactive substances before admission. The average number of previous hospitalisations was 5.4 and the average time from initiation of antipsychotic treatment to the introduction of clozapine into therapy was 7.2 years, while the average of three antipsychotics was administered prior to clozapine. The average duration of hospitalisation was approximately 54 days, with the most common discharge diagnoses being schizophrenia and unspecified nonorganic psychosis (42.4% and 28.6%, respectively).

In Table 2 are shown data on prescribed psychopharmacs on discharge from hospital treatment. The average daily dose of clozapine was 224 mg, and clozapine monotherapy was prescribed in only slightly more than half of patients (53.8%). Adjuvant pharmacotherapy was prescribed in 92% of patients. Within the psychotic polypharmacy, clozapine was the most commonly used with haloperidol (34.9%), followed by fluphenazine (8.4%) and risperidone (2.5%). 76.9% of patients on hospital discharge were prescribed some

Table 1: Sociodemographic and clinical characteristics of patients

Variable	Mean±SD (range)/n(%)
Age	35.54±12.19 (15-67)
Gender – male	146 (61.3)
Education	
Primary	46 (19.3)
Secondary	157 (66.0)
University	35 (14.7)
Employment	
Unemployed	150 (63.0)
Employed	28 (11.8)
Retired	43 (18.1)
Student	17 (7.1)
Marital status	
Not married	192 (80.7)
Married	21 (8.8)
Divorced	24 (10.1)
Widowed	1 (0.4)
Suicidality at admission	84 (35.3)
Suicidal ideas and intentions	54 (22.7)
Suicide attempt	30 (12.6)
Somatic comorbidity	66 (27.7)
Use of psychoactive substances	60 (25.1)
Alcohol	30 (12.6)
Marihuana	22 (9.2)
Opioids	1 (0.4)
Polytoxicomania	7 (2.9)
Number of previous hospitalisations	5.37±5.70 (0-24)
Number of previously applied antipsychotics	3.04±1.42 (0-7)
Time period from starting treatment to introduction of clozapine in therapy (in years)	7.18±7.52 (0-33)
Length of hospital stay (in days)	53.85±28.33 (2-177)
Discharge diagnosis	
Acute schizophrenia-like psychotic disorder	39 (16.0)
Schizophrenia	101 (42.4)
Schizoaffective disorder	31 (13.0)
Unspecified nonorganic psychosis	68 (28.6)

SD=standard deviation

Table 2: Clozapine and adjuvant therapy

Variable	Mean±SD (range)/n(%)
Daily dose of clozapine	223.95±97.73 (25-500)
AMT (clozapine)	128 (53.8)
Adjuvant therapy	219 (92.0)
Haloperidole	83 (34.9)
Fluphenazine	20 (8.4)
Risperidone	6 (2.5)
Chlorpromazine	1 (0.4)
Valproate	157 (66.0)
Lamotrigine	18 (7.6)
Lithium	7 (2.9)
Carbamazepine	1 (0.4)
Benzodiazepine	133 (55.9)
Non-benzodiazepine hypnotics	71 (29.8)
Antidepressants	18 (7.6)
Anticholinergics	21 (8.8)
APP prior to treatment with clozapine	182 (68.1)

SD=standard deviation; AMT=antipsychotic monotherapy; APP=antipsychotic polypharmacy

of the mood stabilisers, most commonly valproate (66%). The frequency of benzodiazepine prescribing was 55.9%, non-benzodiazepine hypnotics 29.8%, antidepressants 7.6%, and anticholinergics 8.8%. Prior to clozapine prescription, in 68.1% of patients were prescribed APP.

The average daily dose of clozapine was significantly higher in patients treated with antipsychotic monotherapy (AMT) (241.3 mg v. 205 mg; U = 5641.000; p = 0.008). The patients treated with clozapine monotherapy were significantly younger and more often primary or university educated and employed. They were significantly more likely to be suicidal and attempt suicide. Also, they rarely had significant somatic comorbidity, and more frequently used psychoactive substances and were discharged under diagnoses F23.2 and F29. Patients treated with the combination of clozapine and other antipsychotics had more days of hospitalisation, a greater number of previous hospitalisations, had significantly more antipsychotics previously administered, and the time period from initiation of antipsychotic therapy to the introduction of clozapine was almost seven years longer. They were also significantly more frequently treated with non-antipsychotic adjuvant therapy, namely benzodiazepines, non-benzodiazepine hypnotics and anticholinergics (Table 3), and almost all (95.4%) were treated with APP before the introduction of clozapine (Table 3).

DISCUSSION

In this paper we have analysed patterns of clozapine administration in patients with some of the schizophrenia spectrum disorders, discharged from hospital treatment during 2018. Of the total number of patients discharged from hospital treatment under the above diagnoses, 23.5% were treated with clozapine, a significantly higher incidence compared to findings from western countries but less than the estimated incidence of TRS of 30%.[11,15,16,27] Patients were treated with an average of about seven years before the introduction of clozapine with three other individual antipsychotics and had an average of about five hospitalisations. Just over half of the patients treated with clozapine treated with AMT, while 46.2% with clozapine were prescribed another antipsychotic, most commonly haloperidol (one third) and fluphenazine, while combination with risperidone (one of recommended in our guide) was prescribed in only 2.5% of patients. Although the guidelines allow clozapine augmentation with other antipsychotics in TRS with poor response to clozapine monotherapy, there is no valid evidence for efficacy, while increasing the likelihood of drug side effects and treatment costs.[28,29] Prior to the introduction of clozapine into therapy, 68.1% of patients were treated with the concomitant use of the other two antipsychotics. This is clear indicator of poor treatment quality and is one of the main factors responsible for delaying the timely administration of clozapine.[9,30] In most European countries, almost half of patients with schizophrenia are hospitalised with prescribed two or more antipsychotics in therapy and most programmes to reduce APP have had no major effect on reducing this pattern of prescribing antipsychotics.[9,31-35] In practice, doctors often remain "stuck" in the process of cross-titration when attempting to replace antipsychotic; often the administration of two antipsychotics at therapeutic doses is considered a better option than the administration of one antipsychotic at a higher than recommended dose; also, pressure on physicians to recover a patient as soon as possible to shorten hospitalisation in circumstances of steadily reducing hospital beds or to meet unrealistic expectations of patients' families often obscures therapeutic goals and is usually the moment when dose escalation and APP occur.[36] There is no evidence that any exaggeration in the doses or number of medications prescribed has an effect in improving the therapeutic response - time is still one of the most important factors in the patient's recovery process.[36] Nevertheless, the main reason for the persistent maintenance of a high incidence of APP in daily practice seems to be the lack of sufficiently effective antipsychotics; every doctor will do anything to help a patient who is not responding to therapy than follow the guidelines.[37] The authors of a large Finnish cohort study suggested that patients who were prescribed more antipsychotics at discharge from their first hospital treatment were among the most severely ill and had a high intrinsic risk of relapse.[38] Findings from our sample indirectly confirm this thesis - patients treated with a combination of clozapine and other antipsychotics had longer hospitalisations, a greater number of previous hospitalisations, and a significantly higher number of antipsychotics were applied to them.

The average daily dose of clozapine was 224 mg and was below the standard acute phase treatment dose, while 17.9% of subjects were below the minimum therapeutic dose given in our guide. In patients treated with APP, the average daily dose of clozapine was even lower and was 205 mg, which is far from the target TRS dose of 400 mg.[14] The use of adjuvant non-antipsychotic therapy is a common practice in the treatment of acute stages of the disease from the

Table 3: AMT with clozapine vs. clozapine as part of APP

Variable	AMT (clozapine) Mean±SD (range)/n(%)	APP Mean±SD (range)/n(%)	t/χ^2/U	p
Age	32.05±12.77 (15-67)	39,61±10.11 (18-64)	-5.007	□0.001
Education			8.099	0.044
Primary	32 (25.0)	14 (12.7)		
Secondary	57 (58.6)	82 (74,5)		
University	21 (16.4)	14 (12.7)		
Employment			13.270	0.004
Unemployed	85 (66.4)	65 (59.1)		
Employed	18 (14.1)	10 (9.1)		
Retired	13 (10.2)	30 (27.3)		
Student	12 (9.4)	5 (4.5)		
Suicidality at admission				0.047
Suicidal ideas/intensions	36 (28.1)	18 (16.4)	6.107	
Suicide attempt	18 (14.1)	12 (10.9)		
Somatic comorbidity	26 (20.3)	40 (36.4)	22.200	0.002
Use of psychoactive substances	40 (31.2)	20 (18.2)	12.211	0.002
Number of previous hospitalisations	3.27±4.62 (0-23)	7.81±5.88 (0-24)	3371.000	□0.001
Length of hospital stay (in days)	50.09±28.56 (2-177)	58.24±27.54 (4-144)	5472.000	0.003
Number of previously applied antipsychotics	2.56±1.42 (0-7)	3.60±1.21 (1-7)	4056.000	□0.001
Time period from beginning of treatment to introduction of clozapine in therapy (in years)	4.42±5.90 (0-31)	10.39±7.95 (0-33)	3357.500	□0.001
Benzodiazepines	63 (49.2)	70 (63.6)	4.988	0.027
Hypnotics	23 (18.0)	48 (43.6)	18.620	□0.001
Anticholinergics	1 (0.8)	20 (18.2)	22.265	□0.001
Discharge diagnose			41.730	□0.001
Acute schizophrenia-like psychotic disorder	31 (24.2)	7 (6.4)		
Schizophrenia	36 (27.3)	65 (59.1)		
Schizoaffective disorder	11 (8.6)	20 (18.2)		
Psychosis NOS	50 (39.1)	18 (16.3)		
APP before clozapine	58 (45.3)	106 (96.4)	70.598	□0.001

AMT=antipsychotic monotherapy; APP=antipsychotic polypharmacy; SD=standard deviation; t=t test; χ^2= Chi-square test; U=Mann-Whitney test

schizophrenic circle.[25,33,39,40] In our sample, as many as 76.9% of patients were prescribed a mood stabiliser, most commonly valproate (66%), while one patient was even prescribed carbamazepine, whose combination with clozapine is absolutely contraindicated. Benzodiazepines have been prescribed in 55.9% of patients, which is also an indicator of poor treatment quality, as this group of drugs in combination with clozapine has an additive sedative effect and is associated with an increase in mortality and suicide in patients with schizophrenia.[41] Anticholinergics were prescribed in 8.8% of patients, and with the exception of one subject, all prescriptions referred to patients on APP. 7.6% of patients were treated with antidepressants, which is significantly less than previous findings in Serbia and foreign studies.[24,42]

Our research had several limitations. First, its retrospective design and inability to evaluate the validity of the diagnoses, to accurately assess the severity of the disease, the patient's compliance, and the reasons for the use of both clozapine and adjuvant antipsychotic and non-antipsychotic drugs. In addition, this research was conducted in a very specific medical facility, in which all agitated, auto and hetero-aggressive, non-cooperative and patients with the most severe forms of the disease from the territory of Belgrade are treating, and its findings are difficult to generalise.

Conclusion

We observed that in treatment of patients with schizophrenia spectrum disorders, clozapine is used less frequently than expected and that there is a significant delay in its use. Most patients are treated with dual antipsychotic therapy with other antipsychotics prior to initiation of clozapine. Also,

clozapine is often prescribed in an inappropriately low dose, and the use of adjuvant therapy is almost universal. Further researches are needed to identify the reasons for the irrational use of clozapine and to implement measures to improve its use and treatment of TRS in everyday clinical practice.

REFERENCES

1. Kane J, Fleischhacker W, Boter H, Davidson M, Vergouwe Y, Keet I, *et al*. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet. 2008;371:1085-97.
2. StroupT, Lieberman J, McEvoy J, Davis S, Swartz M, Keefe R, *et al*. Results of phase 3 of the CATIE schizophrenia trial. Schizophr Res. 2009;107:1-12.
3. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, *et al*. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382:951-62.
4. Vanasse A, Blais L, Courteau J, Cohen AA, Roberge P, Larouche A, *et al*. Comparative effectiveness and safety of antipsychotic drugs in schizophrenia treatment: a real world observational study. Acta Psychiatr Scand. 2016;134: 374-84.
5. Meltzer H, Alphs L, Green A, Altamura A, Anand R, Bertoldi A, *et al*. Clozapine treatment for suicidality in schizophrenia: International Suicide prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60:82-91.
6. Brunette M, Drake R, Xie H, McHugo G, Green A. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. Schizophr Bull. 2006;32:637-43.
7. Wheeler A, Humberstone V, Robinskon G. Outcomes for schizophrenia patients with clozapine treatment: how good does it get? J Psychopharmacol. 2009;23:957-65.
8. Land R, Siskind D, McArdle P, Kisely S, Winckel K, Hollingworth SA. The impact of clozapine on hospital use: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017;135:296-309.
9. Velligan DI, Carroll C, Lage MJ, Fairman K. Outcomes of Medicaid beneficiaries with schizophrenia receiving clozapine only or antipsychotic combinations. Psychiatr Serv. 2015;66:127-33.
10. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, *et al*. 11-year follow up of mortality in patients with schizophrenia: a population based cohort study (FIN 11 study). Lancet 2009;374:620-7.
11. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, *et al*. American Psychiatric Association Practice Guidelines; Work Group on Schizophrenia. Practice guideline for the treatment of patients with schizophrenia, 2nd ed. Am J Psychiatry. 2004;161:1-56.
12. Clinical Guideline 178: Psychosis and schizophrenia in adults: treatment and management. National Institute for health and Care Excellence (NICE). London, UK; 2014.
13. Kreyenbuhl J, Buchanan RW, Dickerson BF, Dixon BL. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2009. Schizophr Bull. 2010;36:94-103.
14. Republička stručna komisija za izradu i implementaciju vodiča dobre kliničke prakse, Ministarstvo zdravlja Republike Srbije. Nacionalni vodič dobre kliničke prakse za dijagnostikovanje i lečenje shizofrenije. Ministarstvo zdravlja. Srbija; 2013.
15. Warnez S, Alessi-Severini Silvia. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry. 2014;14:102.
16. Bachmann CJ, Aagaard L, Bernardo M, Brandt L, Cartabia M, Clavenna A, *et al*. International trends in clozapine use: a study in 17 countries. Acta Psychiatr Scand. 2017:136:37-51.
17. Wheeler AJ, Feetam CL, Harrison J. Pathway to clozapine use: a comprasion between a patient cohort from New Zealand and a cohort from the United Kingdom. Clin Drug Investig. 2014;34:203-11.
18. Grover S, Hazari N, Chakrabati S, Avasthi A. Delay in initiation of clozapine: a retrospective study from a tertiary care hospital in North India. Psychiatry Res. 2015;226:181-5.
19. Robinson DG, Schooler NR, John M, Correl CU, Marcy P, Addington J, *et al*. Medication prescription practices for the treatment of first episode schizophrenia spectrum disorders: data ftom the national RAISE-ETP study. Am J Psychiatry. 2015;172:237-48.
20. Tungaraza TE, Ahmed, W, Chira C, TurnerE, Mayaki S, Nandhra HS, *et al*. Prescribing pattern of antipsychotics for patients with first-episode psychosis: a cross-sectional survey of early intervention team. Ther Adv Psychopharmacol. 2017;7:103-11.
21. Li Q, Xiang YT, Su YA, Shu L, Yu X, Corell CU, *et al*. Clozapine in schizophrenia and its association with treatment satisfaction and quality of life: findings of the three national surveys on use of psychotropic medications in China (2002-2012). Schizophr Res. 2015;168:523-9.
22. Tungaraza TE, Farroq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. Ther Adv Psychopharmacol. 2015;5:88-96.
23. Divac N, Jasović-Gasić M, Samardzic R, Lacković M, Prostran M. Antipsychotic polypharmacy at the University Psychiatric Hospital in Serbia. Pharmacoepidemiol Drug Saf. 2007;16:1250-1.
24. Szkultecka-Debek M, Miernik K, Stelmachowski J, Jakovljević M, Jukić V, Aadamsoo K, *et al*. Treatment patterns of schizophrenia based on the data from seven central and eastern European countries. Psychiatria Danubina. 2016;28:234-42.
25. Jordanova V, Marić NP, Alikaj A, Bajs M, Cavic T, Iosub D. Prescribing practices in psychiatric hospitals in Eastern Europe. Eur Psychiatry. 2011;26:414-8.
26. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical description and diagnostic guidelines. 10th rev. Geneva: World Health Organization; 1992.
27. Kelly DL, Wehring HJ, Gopal V. Current status of clozapine in the United States. Shanghai Arch Psych. 2012;24:110-3.
28. Ballon J, Stroup TS. Polypharmacy in schizophrenia. Curr Opin Psychiatry. 2013;26:208-13.
29. Sthal SM. Antipsychotic polypharmacy, part I: therapeutic option or dirty little secret? J Clin Psychiatry. 1999;60:425-6.
30. Tang Y, Horvitz-Lenon M, Gellad WF, Lave JR, Chang CCH, Normand SL, *et al*. Prescribing of clozapine and antipsychotic polypharmacy for schizophrenia in a large Medicaid program. Psychiatr Serv. 2017;68:579-86.
31. Gallego JA, Bonetti J, Zhang J, Kane JM, Corell CU. Prevalence and correlate of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s to 2009. Schizophr Res. 2012;138:18-28.
32. Dey S, Menkes DB, Obertova Z, Chaudhuri S, Mellsop G. Antipsychotic prescribing and its correlates in New Zealand. Australas Psychiatry. 2016;24:360-4.
33. Jaracz J, Tetera-Rudnicka E, Kujath D, Raczynska A, Stoszek S, Czernass W, *et al*. The prevalence of antipsychotic polypharmacy in schizophrenic patients discharged from psychiatric units in Poland. Pharmacol Rep. 2014;66:613-7.
34. Ritsner MS. Polypharmacy in psychiatric practice: use of polypharmacy in the “Real World”, vol. I. New York: Springer Verlag; 2013.
35. Ritsner MS. Polypharmacy in psychiatric practice: use of polypharmacy in the “Real World”, vol. II. New York: Springer Verlag; 2013.
36. Gelder GM, Andreas CN, Lopez-Ibor Jr JJ, Geddes RJ. New oxford textbook of psychiatry. Oxford University Press; 2009.
37. Christoph U, Correll MD, Shaikh L, Gallego JA, Nachbar J, Olshanskiy V, *et al*. Antipsychotic Polypharmacy: a survey study of prescriber attitudes, knowledge and behavior. Schizophr Res. 2011;131:58-62.
38. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011;168:603-9.
39. Robinson DG, Schooler NR, John M, Correl CU, Marcy P, Addington J, *et al*. Medication prescription practices for the

treatment of first episode schizophrenia spectrum disorders: data from the national RAISE-ETP study. Am J Psychiatry. 2015;172:237-48.
40. Katona L, Czobor P, Bitter J. Real-world effectiveness of antipsychotic monotherapy vs. polypharmacy in schizophrenia: to switch or to combine? A nationwide study in Hungary. Schizophr Res. 2014;152:246-54.
41. Fontanella CA, Campo JV, Phillips GS, Haince-Steelesmith DL, Sweeney HA, Tam K, *et al*. Benzodiazepine use and risk of mortality among patients with schizophrenia. J Clin Psychiatry. 2016;77:661-7.
42. Mao YM, Zhang MD. Augmentation with antidepressant in schizophrenia treatment: benefit or risk. Neuropsychiatr Dis Treat. 2015;11:701-13.

Karličić IS, Stašević M, Đorđević V, Dutina A. Clozapine prescribing patterns in hospitalised patients in everyday clinical practice. Open J Psychiatry Allied Sci. 2020;11:90-5. doi: 10.5958/2394-2061.2020.00019.1. Epub 2020 Apr 17.

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