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Prescription attitudes and practices regarding clozapine among Serbian psychiatrists: results of a nationwide survey

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Abstract

Objective: Despite clozapine being the most effective treatment for treatment-resistant schizophrenia (TRS), a clear explanation as to why it is underutilized and why its initiation is delayed remains unclear. The first aim of the study was to conduct a nation-wide assessment of both the psychiatrists' attitudes of the obstacles for prescribing clozapine as well as their prescription practices. The second aim was to make recommendations, based on the results obtained, for improving the Serbian clozapine guidelines.

Methods: A questionnaire was conducted consisting of two parts. One regarded the clinical characteristics of the psychiatrists, while the second contained questions about indications for clozapine initiation, clozapine prescribing tendencies, and barriers to clozapine use. The questionnaire was sent to 302 Serbian psychiatrists.

Results: With 161 out of the 302 psychiatrists returning the questionnaires, the response rate was 53.3%. Nearly 60% of the psychiatrists treated 10 or more patients with clozapine, with TRS being the most common indication. Only four psychiatrists (2.5%) had no patients currently on clozapine. Psychiatrists indicated that their fear of agranulocytosis (68%) constituted the greatest obstacle for clozapine prescription, followed closely by weight gain (56%), and sedation (39%). Despite their fear of agranulocytosis, only 83.9% of the psychiatrists monitored leukocytes regularly.

Conclusion: In general, psychiatrists in Serbia seem to be confident in prescribing clozapine, even in the absence of clear monitoring guidelines and the possibility of therapeutic drug monitoring. In order to reduce obstacles for clozapine prescription, monitoring laxity, and an overreliance on personal experience, we recommend three modifications of the existing clozapine guideline.

Keywords: antipsychotics, psychopharmacology, psychoses, schizophrenia, side effects

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Introduction

While the evidence that clozapine is, and remains, the only effective drug for treatment-resistant schizophrenia (TRS) is unequivocal, a clear explanation as to why it is not used in all TRS patients remains elusive.[1–4] The debate about lethal neutropenia and agranulocytosis as a serious side effect has been ongoing ever since clozapine was withdrawn in 1974.[5] Although clozapine is effective in patients who had not previously responded to at least two different antipsychotics, its side effects preclude its general prescription. Delayed clozapine initiation is more the rule than the exception.[6] Investigations into the under-prescription of clozapine focus on the attitudes, both of mental health professionals as well as patients. Factors such as patients' refusal to undergo blood tests, prescribers' concerns about clozapine side-effects, or the psychiatrists' personal prescribing experience are contributing factors.[7–14] Recently, the reasons for clozapine under-prescription were

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classified into three categories: barriers related to patients and the drug, clinician-related barriers, and health and system-related factors.[14]

As scientific studies in psychiatrists' prescription attitude and practices toward clozapine in Serbia are absent, we undertook a nationwide survey.

The current state of clozapine prescription in Serbia

In Serbia, the prescription of antipsychotics, including clozapine, is restricted to psychiatrists. Other specialists, such as GPs or psychiatry residents, are not allowed to prescribe any other psychotropic medications than benzodiazepines. Clozapine has been prescribed since the beginning of the 1990s in Serbia.[15,16]

The population of the Republic of Serbia is estimated at 6,982,604 (2018). The number of patients registered with F20-F29 [International Classification of Diseases 10 (ICD-10)] diagnosis varied from 31149 in 2011 (5.4 diagnoses per 1000 adults), 42235 (7.3 per 1000 adults) in 2013, and 38274 (6.79 per 1000 adults) in 2018.[17,18] These data are similar to the internationally reported prevalence of psychotic disorders.[19] Currently, Serbia has 719 practicing psychiatrists: 213 neuropsychiatrists and 506 psychiatrists.[20] There is no information on the number of patients per practicing (neuro-)psychiatrist.

According to Serbian guidelines for schizophrenia, clozapine is to be prescribed in therapy-resistant schizophrenia, that is to say, after an unsatisfactory response to treatment with two antipsychotics, at least one of which is a second generation antipsychotic, in recommended therapeutic doses over the period of 2–8 months for each drug. Prescribing recommendations are to slowly increase the dose from 12.5 to 50 mg/day with a weekly increase of 50–100 mg.

Clozapine accounts for 10.4% of the total sales of all antipsychotics [Anatomical Therapeutic Chemical (ATC) category N05A] in Serbia. The defined daily dose (DDD)/1000 inhabitants/day for clozapine is approximately 0.85. Over the past 4 years, the use of clozapine increased by 16.6%.[17,21]

A search of Serbian literature on clozapine on Medline with the search terms 'clozapine' and 'Serbia' resulted in 33 articles: 9 animal studies, 3 pharmacological *in vitro* studies, 5 reviews, 2 observational studies, 12 epidemiological studies, and 2 randomized controlled trials. Only one study examined Serbian psychiatrists' attitude towards commonly-prescribed antipsychotic drugs.[22] One of the findings was that for only 10% of the clinicians, clozapine would be their drug of choice if they were to treat themselves or their close relatives.

Aims of the study

The main aim of our study was a nation-wide assessment of the Serbian psychiatrists' attitudes of obstacles for prescribing clozapine and of their current prescription practices. The secondary aim was to use the obtained data for a modification and improvement of the Serbian clozapine prescribing guideline.

Material and methods

Participants

Psychiatrists from a total of 13 different facilities in 11 cities were asked to fill out a short questionnaire (see the following paragraph) about clozapine prescription. There was a total of three university clinics, three psychiatric hospitals, and seven psychiatric departments of general hospitals. The selected hospitals and departments are a good cross-sectional representation of all Serbian psychiatric institutions and departments. Private psychiatric institutions were not involved in the study because there are few private psychiatric outpatient clinics, mostly based in Belgrade; the predominant system for mental health care in Serbia is provided by public institutions.

Questionnaire

The questionnaire, newly designed by two authors (DIR and DC) for the purpose of this study, addresses the most relevant specific circumstances of clozapine prescription in Serbia. In the absence of a standardized questionnaire for evaluating attitudes towards clozapine, we selected items and questions from the literature that we considered relevant to psychiatrists, the only mental health professionals who can prescribe clozapine in Serbia, and which targeted their familiarity with the current guideline. The specific circumstances of mental health service in Serbia were considered: no data are available on the number of patients treated per psychiatrist,

Table 1. Short questionnaire for clozapine prescription.

Gender	1. Male 2. Female
How old are you?	_____
How long have you been in the practice of psychiatry?	_____
How many of your patients are currently on clozapine?	1. 0 2. 1–5 3. 6–10 4. More than 10
The indications for clozapine prescription are:	1. Schizophrenia 2. Therapy-resistant schizophrenia 3. Bipolar affective disorder 4. Psychosis in Parkinson's disease 5. All of the above
Frequency of leukocyte monitoring during clozapine treatment.	1. Never 2. Rarely 3. Sometimes 4. Often
How do you begin clozapine treatment?	1. Gradual titration 2. Quick titration
How often do you prescribe clozapine as the only antipsychotic?	1. Never 2. Rarely 3. Sometimes 4. Often
Which drug do you most often use in combination with clozapine?	_____ _____
What do you consider the greatest obstacles for prescribing clozapine?	_____ _____
Do you consider clozapine blood level measurement as useful?	1. No 2. Yes 3. No comment

there are no specialized clozapine in- and outpatient facilities or clinics, and the guideline does not specify the intervals for leukocyte monitoring. The questionnaire is provided in Table 1.

The questionnaires were personally distributed to the psychiatrists during scientific meetings in three sites; in the other nine sites, the questionnaires were sent by mail. All questionnaires were filled out on paper. All psychiatrists were engaged in facilities that provide both out- and inpatient care. As most Serbian clinicians work in both settings, differentiation of clinicians in either in- or outpatient facilities would be nearly impossible.

Ethics statement

The study was approved by the Ethics Committee of Clinical Center Kragujevac (approval code 01/18-460 30; January 2018). Participation was voluntary and anonymous.

Statistics

All data analyses were performed using the SPSS 20 statistical software package (SPSS Inc, Chicago, IL, U.S.A.). Frequencies and percentages were calculated for categorical variables and mean and standard deviations were calculated for continuous variables. The Chi–Square test and *t*-test for independent variables were used, where indicated.

Table 2. Basic demographic and clinical characteristics of the psychiatrists.

		n (%)
Gender	Male	44 (27.3)
	Female	117 (72.6)
Age	29–38	11 (6.8)
	39–48	54 (33.5)
	49–58	69 (42.9)
	59+	23 (14.3)
	Missing data	4 (2.5)
Main treatment setting	Outpatient	74 (46)
	Inpatient	81 (50.2)
	Missing data	6 (3.7)
Workplace	University clinic	59 (36.6)
	Psychiatric hospital	68 (42.2)
	Psychiatric department, General hospital	34 (21.1)
Work experience	<5 years	32 (19.8)
	6–10 years	13 (8.1)
	11–15 years	29 (18.0)
	>15 years	83 (51.5)
	Missing data	4 (2.4)

Results

Out of the total 302 questionnaires that were sent out, a total of 161 were completed and returned, representing a 53.3% response rate. Nearly three-quarters (72.6%) of the responding psychiatrists were women aged between 39–58 years. Over 50% of the respondents had at least 15 years of working experience. The sociodemographic and clinical characteristics of the psychiatrists are shown in Table 2.

Clozapine prescription practices

Nearly 60% of the psychiatrists treated 10 or more patients with clozapine, with TRS being the most common indication. Four psychiatrists had no patients currently on clozapine. Clozapine initiation was largely (95%) gradual, with clozapine being the only prescribed antipsychotic drug in the majority (63.3%) of the patients (see Table 3 for all information on clozapine prescription practices).

No statistically significant difference in the number of patients receiving clozapine between the more experienced (>15 years of practice) and less experienced psychiatrists was found ($\chi^2 = 3.35$, $p = 0.341$). The number of patients on clozapine was not influenced by university *versus* non-university settings.

The drugs most commonly co-prescribed with clozapine are given in Table 4. Clozapine was most commonly prescribed in combination with another antipsychotic, followed by mood-stabilizers, while anxiolytics and antidepressants were prescribed more rarely.

Obstacles for prescribing clozapine

The obstacles for clozapine prescription centered on seven predominant factors depicted in Figure 1. Psychiatrists marked fear of possible

Table 3. Clozapine prescription practices.

1. How many of your patients are currently on clozapine?	0 patients	2.5%
	1–5 patients	19.9%
	6–10 patients	15.5%
	>10 patients	59.6%
	No answer	2.5%
2. For which indications do you prescribe clozapine? (multiple answers possible)	Schizophrenia	57.1%
	Therapy-resistant schizophrenia	88.2%
	Bipolar disorder	50.3%
	Psychosis in M. Parkinson	64.0%
	All of the above	41.6%
3. How do you begin clozapine treatment?	Gradual titration	95.6%
	Quick titration	1.2%
	No answer	3.1%
4. How often do you prescribe clozapine as the only antipsychotic?	Never	1.6%
	Rarely	8.2%
	Sometimes	26.7%
	Often	63.3%

Table 4. Drugs most commonly prescribed together with clozapine*.

Antipsychotics	69.4%
Fluphenazine	1.2%
Haloperidol	36.7%
Sulpiride	3.1%
Risperidone	16.8%
Long-acting injectables	6.2%
Other antipsychotics	36.0%
Antidepressants	21.1%
Mood stabilizers	36.7%
Anxiolytics	25.5%
Anticholinergics	3.7%

*Clinicians were given an option to write down more than one drug that they commonly prescribe together with clozapine.

agranulocytosis (68%) as the greatest obstacle, followed closely by weight gain (56%) and sedation (39%).

Leukocyte monitoring practice. Two (1.2%) psychiatrists answered that they never monitor leukocytes and differential when prescribing clozapine, one (0.6%) did, but only 'rarely', 23 (14.3%) 'sometimes', and 135 (83.9%) 'often'. No quantifications of the answers were required.

Therapeutic drug monitoring (TDM). A majority of psychiatrists, 132 (82.0%), indicated that they consider measurement of clozapine serum levels as useful, eight (5.0%) answered they didn't; the remaining 21 (13.1%) psychiatrists did not answer this question.

Discussion

Our sample consisted of 161 Serbian psychiatrists from 13 different facilities all over the country. Compared with other studies in prescribers'

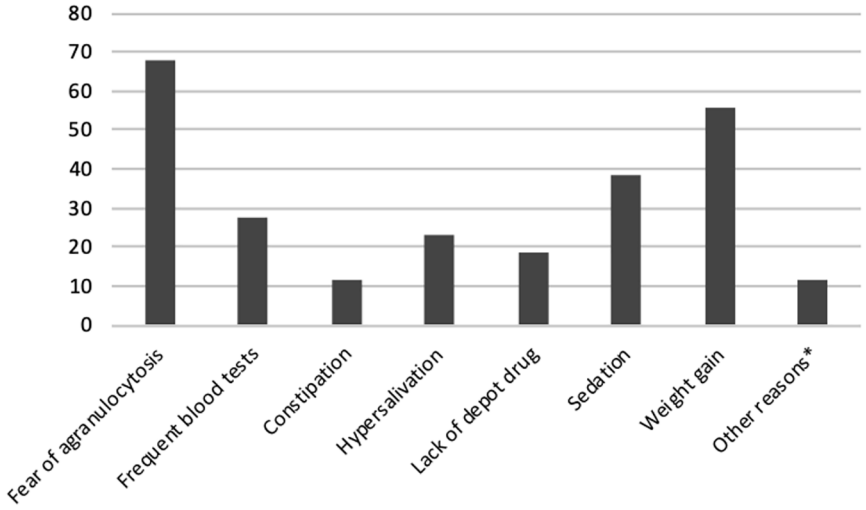

Figure 1. Most commonly reported obstacles for clozapine prescription.
*Among the variety of other reasons mentioned were seizures, loss of consciousness, drowsiness, EEG testing, metabolic syndrome, confusion, hyperlipidemia and hyperglycemia, postural hypotension, and hypersomnia.

Table 5. Studies evaluating psychiatrists' attitudes towards clozapine.

	Daod *et al.*[9]	Grover *et al.*[14]	Nielsen *et al.*[7]	Latas *et al.*[*22]	Kelly *et al.*[23]	This study
Response (%)	47.50	16.2	43.1	–	32	53.3
Number (*n*)	295	548	100	90	277	161
Age (years)	–	38.9 ± 10.7	54	46.1 ± 10.1	–	49.9 ± 7.9
Sex (male) (%)	54.20	–	–	32.2	53	27.3
Working experience (years)	–	12.6 ± 10.1	20	19.4 ± 10.5	–	16.5 ± 9.3

*Study of psychiatrists' attitudes towards antipsychotics *in general.*

attitudes (see Table 5), this study is characterized by the highest response rate, the highest mean age, and the highest proportion of female respondents.

The first major finding of our study is that nearly all clinicians (97.5%) reported prescribing clozapine to their patients, with nearly 60% reporting currently treating 10 patients or more. TRS was by far the most common indication for clozapine prescription (88.2%). Clozapine is initiated by titrating slowly (95.7%) and most respondents noted that they performed blood tests often for patients receiving clozapine (83.9%). This indicates that clozapine is widely-prescribed in the clinical setting in Serbia, even though the guidelines for clozapine prescription are not rigorous.

The Serbian clozapine guidelines do not mandate the measurement of clozapine serum levels. Currently, measuring clozapine serum levels is not routinely performed in any institution in Serbia; the only exception being toxicological measurements for especially-indicated cases. Considering the fact that 82% of clinicians found clozapine serum measurement useful, a simpler method might contribute to improved clozapine prescription. A Serbian study is underway using the dried blood spot (DBS) technique[24] that evaluates the measurement of clozapine levels on adequate dosing, patient satisfaction, and patient drug adherence.

The characteristics of the four clinicians with no current patients on clozapine show that only one had more than 5 years of experience. In contrast, Nielsen *et al.*,[7] in their study of psychiatrists' knowledge of clozapine, found that all seven psychiatrists, who never prescribed clozapine, had more than 5 years of clinical experience. However,

the number of four psychiatrist in our study is too small for statistical analysis and interpretation.

Clozapine in combination with other psychotropic drugs

Even though polypharmacy can complicate treatment through additive side effects, which in itself is a relevant topic when prescribing clozapine, it has in the past been argued that TRS sometimes requires the addition of other antipsychotics or other types of psychotropic drugs to ongoing clozapine.[25,26] However, while the debate about the efficacy of additional therapy to clozapine is ongoing,[27] clozapine plasma levels remain the first thing that is needed to diagnose clozapine resistance. Given the highly divergent plasma levels that have been shown on the same clozapine dosage,[28] this requires adequate measurement of the clozapine plasma levels. A study that included 99 patients with TRS who were without clozapine found that 35% had subtherapeutic antipsychotic plasma levels, and the lack of plasma level testing could increase unwarranted polypharmacy.[29] In the absence of the possibility of measurement of blood levels of prescribed antipsychotic drugs, as is the case in Serbia, issues such as non-compliance, subtherapeutic dosing, and adequate or possibly toxic plasma levels, cannot be determined nor ruled out. In our sample, we found that the most prescribed combination with clozapine was haloperidol, (the prescription of first-generation antipsychotics remains a trend in Serbia) which we consider as a compromise, a way out of the uncertainty psychiatrists experience: given the uncertainty about clozapine levels, they opt for certainty by dosing clozapine low, in addition to familiar haloperidol treatment.

Major obstacles for prescribing clozapine

An overview of the major obstacles from this study and other studies evaluating clinician attitudes towards clozapine is given in Table 6. Three studies are not included: in one study,[8] the phrasing of the questionnaire was too general and vague. A second study[30] conducted a provider-level analysis in general, instead of asking clinicians individually, while a third study[31] examined the decision-making process of initiating clozapine, but not the prescribers' attitudes.

Looking at the results from the perspective of clozapine's four potentially lethal side-effects- agranulocytosis, diabetic keto-acidosis, gastrointestinal hypomotility and myocarditis,[33,34]we see that most psychiatrists in our study considered the possibility of agranulocytosis as the biggest obstacle in prescribing clozapine, which is similar to the findings of other studies.[8,9] However, while concern about agranulocytosis was present in 68% of the participants, only 28% considered blood tests obligatory.

An awareness of gastrointestinal hypomotility and myocarditis, two potentially lethal side-effects of clozapine, is conspicuously absent. Gastrointestinal hypomotility has a nearly identical incidence rate as agranulocytosis (4–8‰ and 3.6–8‰ respectively), but the mortality rate is 3–12 times higher.[33]

The lack of concern about potentially fatal myocarditis is remarkable, as even though the incidence is lower outside of Australia, it is still considered an important potential obstacle in the initial phase of clozapine treatment.[33,34]

Frequent blood tests were not considered as an important obstacle to clozapine prescription in our sample, which is unlike several recent studies in which clinicians raised concerns about nonadherence to blood work, the burden of blood draws, and the increased need for monitoring.[10,23] A study examining the patients' subjective well-being under clozapine found that patients did not object to frequent blood monitoring.[35] Several other studies have reported that discontinuation of clozapine due to dislike of blood monitoring occurs very rarely.[36,37] In addition, blood testing does not appear to be an important barrier to the initiation of clozapine.[38]

The other major obstacle that was commonly mentioned, despite not being life-threatening, was weight gain (55.9%). This is a justified concern, because clozapine does cause significant weight gain, among most of all second-generation antipsychotics[39] and lipid abnormalities lead to increased risk of metabolic syndrome.[40] However, the largest study so far, with 62.250 patients followed over a period of 20 years, found lowest physical comorbidity and mortality in clozapine-treated patients.[41] This often leads to a difficult situation requiring balancing risks and benefits in determining whether there is an adequate substitute for clozapine in TRS.

The 39% of the clinicians who considered sedation as an important obstacle in clozapine

Table 6. Comparison of obstacles towards prescribing clozapine from various studies.

	Daod *et al.*[9]	Grover *et al.*[14]	Nielsen *et al.*[7]	Tungaraza and Farooq[32]	This study
Agranulocytosis (%)	71.2	38	30	–	68
Need for monitoring (%)	–	50.5	60	74	27
Seizures (%)	–	23.5	–	–	–
Metabolic/weight gain (%)	–	38.5	75	80	56
DM (%)	9.5	–	–	–	–
Other (%)	n.a.	23.5	26	–	12
Cardiac issues (%)	34.2	–	25	–	–
Myocarditis (%)	34.2	–	–	–	–
ECG-changes (%)	8	–	–	–	–
Constipation (%)	4.7	–	–	–	12
Hypersalivation (%)	3.4	–	26	–	23
Sedation (%)	–	–	30	–	39

DM, diabetes mellitus; ECG, electrocardiogram.

prescription is far less than the 79% of patients who reported sedation as a significant side-effect of clozapine.[35] Patients' acceptance of clozapine is likely to be improved by offering the opportunity to start clozapine at home and by improved education about the therapeutic benefits of clozapine and the management of its adverse effects.[38,42]

Despite the absence of a Serbian guideline for clozapine prescription, only one psychiatrist considered the 'lack of guidelines' as a major obstacle for clozapine prescription. This suggests that clinicians in Serbia use their personal experience as their own clozapine-treatment guidelines. This is consistent with the results of Gee *et al.*,[8] who, in the presence of clozapine guidelines, were unable to find a correlation between the level of awareness of the guidelines and prescription patterns. This lack of correlation was not unique for clozapine: after publication of national prescription guidelines, the prescription of psychotropics effectively remained unchanged, suggesting that psychiatrists tend to use their clinical judgment in prescribing these medications.[43,44]

A 'fear of clozapine' is figuratively described as one of the main obstacles towards prescribing this drug.[45] Certainly, safety concerns do emerge when discussing clozapine; chiefly, these are the fear of neutropenia or agranulocytosis.[34,46] Multiple recent studies have shown and confirmed the earlier finding by Tiihonen[40,42] that clozapine has the lowest mortality rates of all antipsychotics. Cohen *et al.* have shown that, with proper administration, there is little to fear when prescribing this drug. The mortality of cases effected by agranulocytosis ranged from 2.2% to 4.2% with proper monitoring, to 34% without monitoring.[34,47] Recently, a mandatory training program for prescribers, which aims to improve the knowledge about clozapine prescription was proposed in order to overcome these issues.[48]

Here, we outline our proposed modifications of the national Serbian guidelines. Based on the international literature and the responses we obtained from this survey, we propose three modifications. Firstly, we suggest changes to leukocyte monitoring. While the frequency is described adequately in the existing guidelines, we propose change the quality of the recommendation of leukocyte monitoring from voluntary to mandatory. Secondly, we suggest changes to blood sampling: we propose to add leukocyte and

differentiation from capillary sampled blood as a reliable alternative for the current venously sampled blood. Thirdly, the measurement of clozapine plasma or blood levels should be encouraged as a valuable instrument that adds to the information clinicians need for adequate dosing of clozapine in their patients. This can be conducted either in venous blood samples or *via* the dried blood spot (DBS)- technique; here, a filter, after collecting a drop of capillary blood that is dried for 3 h, is sent to a specialized laboratory for clozapine measurement.[24,49]

Our study has several strengths. To begin with, the study is the first to gather novel data on psychiatrists' attitudes and practices towards clozapine in Serbia. Secondly, the study is based on a representative sample of the different psychiatric facilities in Serbia. Thirdly, the relatively high response rate of 53.3% strengthens the reliability of the outcome of this study.

Our study also has several limitations. The main limitation is that the questionnaire, after it had been designed, was not tested or validated. The second limitation is about the sampling process: as sampling was not randomized and the representativeness of the sampled participants cannot be guaranteed. Our conclusions, are, therefore, preliminary. A third limitation is the absence of data on the number of patients for in- and outpatient facilities and clinicians.

In general, psychiatrists in Serbia seem to be confident in prescribing clozapine, even in the absence of monitoring guidelines and the option of therapeutic drug monitoring. In order to reduce obstacles for clozapine prescription and monitoring laxity, we must reduce the overreliance on personal experience and diminish uncertainties by providing clear treatment and monitoring guidelines. Technological innovations, such as Hemocue, and DBS, can help, as well as a national clozapine expertise center.[50,51]

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Conflict of interest statement

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