Patients’ and psychiatrists’ stance on the current state of pharmacological depression treatment in Serbia and prospects of introduction of personalized pharmacotherapy and its potential effects

Aleksandra Jeremić¹, Filip Milosavljević¹, Ana Opanković², Marin Jukić¹,³*

¹ University of Belgrade – Faculty of Pharmacy, Vojvode Stepe 450, Belgrade, Serbia
² Clinic of Psychiatry, Clinical Center of Serbia, Pasterova 2, Belgrade, Serbia
³ Department of Physiology and Pharmacology, Karolinska Institutet, 17177 Solna, Sweden

* Corresponding author: Marin M. Jukic; e-mail: marin.jukic@pharmacy.bg.ac.rs

Abstract:

The use of antidepressants has been steadily increasing. Even though the amount of evidence on the usefulness of personalized drug dosing in depression treatment is growing, there is still resistance and skepticism among physicians and regulators regarding the implementation of CYP450 genotyping and therapeutic drug monitoring in psychiatric clinical practice. The aim of this study was to quantify the opinions of psychiatrists and patients from three large psychiatric clinics in Belgrade, Serbia, and to examine what requirements need to be met to make changes in clinical guidelines or recommendations. All participants completed an anonymous questionnaire that was developed at the Faculty of Pharmacy, University of Belgrade. Fourteen practicing psychiatrists and 30 patients currently treated for depression completed the questionnaire. Distributions of opinion scores were compared between the psychiatrists and patients upon the visual inspection of the violin plots. Our results show that psychiatrists predominantly have a positive opinion on personalized dosing in psychiatry and that patients are most likely to comply with new approaches in depression pharmacotherapy. However, due to the long time needed for regulatory change, it is very unlikely that personalized dosing would be rapidly implemented in clinical practice, even if adequate evidence was to emerge.

Key words: major depressive disorder, precise medicine, therapeutic drug monitoring, Pharmacogenetics

https://doi.org/10.5937/arhfarm72-37613
**Introduction:**

Affective disorders, with depression leading the way, are a major contributor to the morbidity caused by diseases worldwide (1), and the use of antidepressants (ADs) has been steadily increasing over the last decade (2). Drugs from this group act predominantly on monoaminergic transmission and reduce a spectrum of symptoms – from affective and will-instinctive to cognitive psychopathology. Selective serotonin reuptake inhibitors (SSRIs), despite their limitations, are the cornerstone of modern anxiolytic and antidepressant pharmacotherapy (3).

Despite increasing numbers of treatment options, substantial gaps in care remain. These could be attributed to three core problems: (i) only about 50% of depressions are correctly diagnosed by the treating physician (4); (ii) fewer than 50% of the correctly diagnosed patients receive adequate treatment with adequate doses and treatment duration (4), and (iii) fewer than 35% who receive an adequate treatment achieve remission with the first applied antidepressant drug (5).

From the perspective of the clinician, the choice of treatment is particularly challenging for a number of reasons. None of the available treatments is a panacea for all patients, the range of options is bewilderingly wide, and clinical evidence does not give a solid basis for selection. Therefore, clinicians often prescribe an AD on the basis of individual expertise or personal opinion (6).

However, since the development of successful and applicable psychiatric drugs has been at a near standstill for a very long time, it is of utmost importance to utilize the psychiatric drugs currently available on the market as effectively as possible. One important aspect is precise dosing, since doses required to achieve optimal blood levels of many antidepressants and antipsychotics vary substantially among patients (7). Indeed, dose-response and dose-tolerability relationships were established for antipsychotics (8), and antidepressants (9). Consequently, population-based dosing leads to a significant proportion of patients being either under- or over-exposed (10) to the drug. Finally, the therapeutic window is relatively well-defined for many psychiatric drugs by the recently published consensus guidelines for TDM, based on positron emission tomography, pharmacokinetic and clinical studies (7), and TDM is also determined to be a cost-effective tool (11). Still, therapeutic drug monitoring (TDM) is most commonly utilized just for a limited number of drugs (12); for example, most clinical guidelines for antidepressants recommend TDM just for tricyclic antidepressants (TCA), mainly to reduce the risk of adverse reactions (12).

Even though the amount of evidence on the usefulness of the personalized drug dosing in depression treatment is growing, there is still a lot of resistance and skepticism among physicians and regulators regarding the implementation of CYP450 genotyping and therapeutic drug monitoring in psychiatric clinical practice. It is important to note that, although many genetic and non-genetic factors impact pharmacotherapy outcomes in psychiatry on an individual level, CYP450 genotyping was chosen as a focus of this
survey due to it being one of the most important pharmacogenomic factors in psychiatry (7).

To our knowledge, to this day there have been no studies on patients’ and psychiatrists’ attitudes of the current state of pharmacological therapy of depression and the prospects of implementation of personalized dosing in psychiatric practice in Serbia. Therefore, the aim of this study was to quantify the opinions of both psychiatrists and patients from three large psychiatric clinics in Serbia: the Institute of Mental Health in Belgrade, University Psychiatric Clinic in Belgrade and Psychiatry Clinic of the Military Medical Academy, Belgrade. Our secondary aim was to discuss what requirements need to be met to make changes in clinical guidelines or to introduce new dosing recommendations in drug labels of antidepressants.

**Experimental part:**

All participants completed an anonymous questionnaire that was developed at the Department of Physiology, Faculty of Pharmacy, University of Belgrade.

The questionnaire was divided into three parts: (i) Ten questions (Questions 1 through 10: Q1 - Q10) that were aimed at both psychiatrists and patients; (ii) two patient-specific questions (Question 11 and Question 12: Q11 and Q12) and (iii) two psychiatrist-specific questions (Question 13 and Question 14: Q13 and Q14). Seven questions (Q1-Q7) regarded the current state in the psychiatry practice in Serbia and issues such as psychiatrists’ prescription habits, patients’ compliance, social stigma, etc. The other seven questions (Q8-Q14) regarded personalized dosing in depression treatment. Every question consisted of a statement for which participants had to give one of the following semi-quantitative opinion scores: -3 (Strongly disagree); -2 (Disagree); -1 (Mostly disagree); 0 (Neutral/No strong opinion); +1 (Mostly agree); +2 (Agree) and +3 (Strongly agree). The full questionnaire is presented in Table I.

Distributions of opinion scores were compared between the psychiatrists and patients upon the visual inspection of the violin plots.
**Table I** Complete questionnaire on the current state of depression treatment in Serbia and prospects of antidepressant dose personalization. Opinion scores: -3 (Strongly disagree); -2 (Disagree); -1 (Mostly disagree); 0 (Neutral/No strong opinion); +1 (Mostly agree); +2 (Agree) and +3 (Strongly agree).

**Tabela I** Kompletan upitnik o trenutnom stanju farmakoterapije depresije u Srbiji i implementaciji personalizacije doze antidepresiva. Skor: -3 (Izričito se ne slažem); -2 (Ne slažem se); -1 (Uglavnom se ne slažem); 0 (Neutralno/Nemam mišljenje); +1 (Pretežno se slažem); +2 (Slažem se), +3 (Izričito se slažem).

<table>
<thead>
<tr>
<th>Claim</th>
<th>Opinion score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: Psychiatrists are motivated and have enough time to commit to every patient.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q2: Psychiatrists prescribe antidepressants easily and too often.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q3: During depression treatment, patients adhere to psychiatrists’ directions and recommendations.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q4: Patients are willing to start taking antidepressants when their psychiatrist recommends it.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q5: Patients are disinclined to speak publicly about their illness and therapy because they fear being discriminated.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q6: Patients act timely in asking for professional help when they notice symptoms of depression.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q7: It is common practice for a patient to ask for a second opinion regarding their depression therapy.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q8: Monitoring the concentration of the drug in the blood is important for patients who take antidepressants.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q9: An individual's genetics may predetermine a reaction to a certain antidepressant.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q10: It is realistic to introduce therapeutic drug monitoring and genetic testing as a part of psychiatric treatment in today’s Serbia.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q11: As a patient, I have at least once increased the dose of an antidepressant without consulting my psychiatrist.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q12: As a patient, I have at least once discontinued antidepressant therapy without consulting my psychiatrist.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q13: As a psychiatrist, I have recognized the need for drug dose personalization to a greater extent than recommended by the guidelines.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
<tr>
<td>Q14: As a psychiatrist, I have noticed that the time when non-adherence occurs most often is shortly after the initiation of the drug.</td>
<td>-3 -2 -1 0 1 2 3</td>
</tr>
</tbody>
</table>
Results:

A total of 44 participants completed the questionnaire; 14 of them were practicing psychiatrists, and 30 were patients currently being treated for depression. The numbers of participants surveyed per clinic were: (i) two psychiatrists and 6 patients at the Institute of Mental Health, Belgrade; (ii) nine psychiatrists and 17 patients at the Psychiatry Clinic of the Clinical Center of Serbia, Belgrade and (iii) three psychiatrists and 7 patients at the Psychiatry Clinic of the Military Medical Academy, Belgrade.

The results are presented in the Figure 1 as violin plots which represented histograms of the semi-quantitative opinion score distribution across the groups.

![Survey results](image)

**Figure 1.** Violin plots of the survey results. The width of a violin plot indicates the distribution of individuals across different opinion score.

Patients had a slightly more positive opinion on the psychiatrists’ ability to provide good treatment to the patients in the everyday practice, as their opinion on Q1 mostly varied between “Agree” and “Highly agree”, while the opinion of psychiatrists mostly varied between “Mostly agree” and “Agree”. Overall, the opinions on psychiatrists’ performance were clearly positive, with only a few negative opinions in both groups.

The opinion on Q2 varied drastically within both groups, but most patients stated that there is no excessive drug prescription in the treatment of depression. As for psychiatrists, stratification in two sub-groups could be observed: 40% of psychiatrists...
were grouped around the “Disagree” option, while 60% of psychiatrists mildly agreed that the usage of antidepressant is often unjustified.

A great majority of patients and psychiatrists answered positively to Q3, but the strength of the opinion varied between the groups. Namely, most of the patients answered with “Agree” or “Highly agree”, while most of the psychiatrists answered with “Mostly agree” when asked whether patients tend to follow proposed directions. A similar tendency was observed with Q4, which referred to the willingness of patients to comply with the pharmacological treatment: a great majority of both groups gave positive answers that were stronger in patients and more moderate in psychiatrists.

Q5 was focused on the social stigma that exists around mental illness in the general society in Serbia, and both groups agreed that the stigma exists, but the opinions on the extent of that stigma varied significantly among the surveyed individuals within both groups.

Regarding the question of whether patients react timely when seeking professional help for psychiatric problems, without waiting and potentially risking further progression of symptoms (Q6), psychiatrists almost unanimously answered that patients tend to delay seeking psychiatric help. On the other hand, patients were stratified into two groups: about one third of patients agreed with psychiatrists, while about two thirds of patients gave the opposite answer.

Next, our results show great variability within groups regarding Q7. A majority of psychiatrists had neutral opinions on how often patients seek a second psychiatric opinion, while the surveyed patients revealed that a slight majority of them do not ask for a second opinion, but also that there is a slight number of them that do.

When asked about the importance of therapeutic drug monitoring (Q8) and genotyping (Q9) in psychiatry, psychiatrist gave similar opinions, stating that most of them find these procedures important or highly important. It is important to note that a certain number of psychiatrists were skeptical about the importance of therapeutic drug monitoring. As for the patients, their opinions varied between positive and neutral. When asked for an opinion on whether it would be realistic to deploy genotyping and therapeutic drug monitoring in today’s Serbian clinical practice of depression, opinions varied greatly. Even though opinions varied, the majority of patients had a neutral opinion. On the other hand, out of 14 surveyed psychiatrists 8 had an optimistic view of this issue, 4 gave neutral opinions, and 2 were skeptical about the prospects of implementing personalized dosing.

Patient-specific questions revealed that a great majority of the surveyed patients strongly affirmed that they had never decided to stop antidepressant therapy (Q11), nor had they increased the dose without consulting their psychiatrist (Q12). Only a minority of patients (5/30) answered that they had initiated a dose increase, and an even smaller number (4/30) reported that they had stopped the therapy on their own.

As for the psychiatrist-specific questions, a great majority of the subjects stated that they recognized the need for antidepressant dose personalization, while a minority
remained neutral (Q13). Moreover, concerning the greater incidence of non-adherence at the beginning of antidepressant therapy (Q14), psychiatrists’ opinion varied greatly, with both positive and negative opinions. Still, a slight majority was in favor of agreeing with the statement.

**Discussion:**

Our research managed to quantify the opinions of both psychiatrists and patients from three large psychiatric clinics in Serbia regarding the current state of pharmacological therapy of depression and the prospects of implementation of personalized dosing in psychiatric practice in Serbia.

The results suggest that psychiatric patients in Serbia have a very high opinion of the psychiatrists and their commitment, and that patients claim that they are highly willing to comply with the psychiatrists’ directions. This is further highlighted by the fact that most of the surveyed patients claimed they do not usually ask for a second opinion regarding depression treatment. Furthermore, the surveyed patients showed a predominantly positive opinion on antidepressants and their usage in psychiatric practice. There are some indications that patients’ responses may be slightly overenthusiastic, since there is slight misalignment between patients’ and psychiatrists’ opinions regarding patients’ compliance. The most pronounced difference in opinions was observed in Q6, where psychiatrists claimed that patients do not seek help on time, while most patients disagreed. A probable explanations for this may be either the unwillingness of most patients to admit their delay in seeking help, or different definitions of “optimal time to seek help” between patients and psychiatrists. Still, even when these discrepancies are taken into account, the impression that psychiatric patients in Serbia tend to follow their doctors’ directions in most cases prevails.

Next, a divide between psychiatrists on whether antidepressants are overprescribed or not is expected, since there is high variability among psychiatrists in antidepressant prescription habits (3, 13). A great majority of psychiatrists claimed that they do recognize the need for dose personalization in depression treatment by means of therapeutic drug monitoring and genotyping. This is in accordance with our recently published results (10, 14, 15, 16) on an altered drug blood levels in individuals with variant enzyme capacity to metabolize such drugs. Still, these results have several limitations such as (i) the unknown impact of other genetic and environmental factors on clinical outcomes of pharmacotherapy, (ii) the fact that the relationship between drug concentration and clinical outcomes for many drugs is still not conclusively determined (17, 18, 19), and (iii) the problem of translation of genetic test results into clinical recommendations (20). All these factors may be a source of skepticism and caution among certain physicians.

As for the prospects of employing these techniques in everyday practice, psychiatrists were more skeptical on average; their skepticism probably originates from the notion that there are many unresolved challenges in everyday psychiatric practice in Serbia that need to improve before the onset of personalized antidepressant dosing. The
patients’ opinion on dose personalization was neutral on average, indicating that most patients are probably not familiar with therapeutic drug monitoring and genetic tests and their potential utility in psychiatry.

Personalized drug dosing could be implemented in clinical practice in Serbia either by the implementation of dosing recommendations into the National guidelines for depression treatment (21), published by the national Ministry of Health, or by the implementation of dosing recommendations into drug labels by the Medicine and Medical Devices Agency of Serbia. Publication of the Guideline on good pharmacogenomic practice EMA/CHMP/718998/2016 (22) demonstrates the willingness of regulatory bodies such as EMA to take new pharmacogenetic findings into account as they emerge. Nevertheless, considering the way of worldwide dealing of marketing authorization holders with regulatory bodies, any regulatory change would take a long time. There is general regulatory alignment, although there are differences in the timeframes of approval; the FDA is significantly faster than the EMA, since the EMA’s timelines formally require two steps, namely (i) the opinion of the Committee for Medical Products for Human Use, followed by (ii) decisions by the European Commission (23). Introducing changes to national drug labels requires alignment with larger regulatory bodies, which would significantly extend the time needed, even if strong evidence was formed about the utility of precise dosing of antipsychotics and antidepressants. Finally, National guidelines for depression treatment could bypass this process and ensure more rapid implementation, but this is very unlikely, since this document was last updated almost a decade ago.

Overall, the introduction of precise psychiatry into clinical practice is a challenging but ongoing process that, besides strong evidence of its benefits, also requires the education of health professionals, promotion by institutions and regulatory bodies and overcoming economic and ethical barriers (24). Our results demonstrate that psychiatrists in Serbia predominantly have a positive opinion on personalized dosing in psychiatry and that patients are most likely to comply with new approaches in depression pharmacotherapy. Nevertheless, it is unlikely that personalized dosing recommendations would be rapidly implemented in clinical practice, if crucial evidence was to emerge.

**Acknowledgement:**

This work has been financially supported by the Science Fund of the Republic of Serbia (PROMIS-PsyCise grant ID 6066800 to Marin Jukić, Filip Milosavljević, Aleksandra Jeremić, Bojan Marković and Bojan Batinić).
References:


Stav pacijenata i psihijatara o trenutnom stanju farmakoterapije depresije u Srbiji i mogućnosti uvođenja personalizovane farmakoterapije i njenim potencijalnim efektima

Aleksandra Jeremić¹, Filip Milosavljević¹, Ana Opanković², Marin Jukić¹,³*

¹ Univerzitet u Beogradu – Farmaceutski fakultet, Vojvode Stepe 450, Beograd, Srbija
² Psihijatrijska klinika, Klinički centar Srbije, Pasterova 2, Beograd, Srbija
³ Odsek za fiziologiju i farmakologiju, Karolinska Institutet, 17177 Solna, Švedska

* Autor za korespondenciju: Marin M. Jukic; e-mail: marin.jukic@pharmacy.bg.ac.rs

Kratak sadržaj

Upotreba antidepresiva je u stalnom porastu. Iako raste količina dokaza o korisnosti personalizovanog doziranja lekova u lečenju depresije, još uvek postoji veliki otpor i skepticizam među lekarima i regulatorima u pogledu primene CYP450 genotipizacije i terapijskog praćenja lekova u psihijatrijskoj kliničkoj praksi. Cilj ove studije je bio da se kvantifikuju mišljenja psihijatara i pacijenata sa tri velike psihijatrijske klinike u Beogradu, u Srbiji, i da se ispitati koji zahtevi treba da budu ispunjeni da bi se izvršile promene u kliničkim smernicama ili preporukama za doziranje antidepresiva. Svi učesnici su popunili anonimni upitnik koji je izrađen na Farmaceutskom fakultetu Univerziteta u Beogradu. Upitnik je popunilo 44 učesnika, od kojih 14 psihijatara i 30 pacijenata koji se trenutno leče od depresije. Dodatno je kontaktiran i jedan stručnjak za farmakologiju. Distribucija ocena mišljenja je poređena između psihijatara i pacijenata nakon vizuelnog pregleda violin dijagrama. Naši rezultati pokazuju da psihijatri uglavnom imaju pozitivno mišljenje o personalizованom doziranju u psihijatriji i da bi se pacijenti većinski pridržavali novih pristupa u farmakoterapiji depresije. Međutim, malo je verovatno da bi regulatorna tela u Srbiji brzo ažurirala svoje smernice, čak i ako bi se pojavili adekvatni dokazi.

Ključne reči: veliki depresivni poremećaj, precizna medicina, terapijsko praćenje lekova, Farmakogenetika