

IS TREATMENT-RESISTANCE IN PSYCHIATRIC DISORDERS A TRAP FOR POLYPHARMACY?

Miroslava Jašović-Gašić

Faculty of Medicine, University of Belgrade, Academy of Medical Science, Serbian Medical Society, Belgrade, Serbia

SUMMARY

Background: Nowadays, more and more mental health professionals manage patients who fail treatment for major psychiatric disorders. There is not a consensus on how to deal with treatment-resistance patients, but usually psychiatrists result to polypharmacy.

Method: In reviewing the evidence based clinical research we will try to answer some questions about treatment-resistant psychiatric disorders. Treatment-resistant symptoms complicate the clinical course of all psychiatric disorders especially schizophrenia, causing the patients not to reach the therapeutical goal and enter remission. In consequence, polypharmacy is used to try to deal with the remaining symptoms, raising other issues.

Summary: We will try to deal with this problematic issue through clinical studies and major research done to try and answer the question posed.

Key words: treatment resistance – polypharmacy – schizophrenia - psychiatric disorders

* * * * *

INTRODUCTION

Nowadays, more and more mental health professionals manage patients who fail treatment for major psychiatric disorders. Theraporesistency or treatment resistance is defined as the lack of therapeutic response in the application of two drugs from the same group in adequate doses (recommended optimal dose) in a certain period of time (varies from two to eight weeks). There is not a consensus on how to deal with treatment-resistance patients, but usually psychiatrists result to polypharmacy. We will try to deal with this problematic issue through clinical studies and major research done to try and answer the question posed.

THE CONCEPT OF TREATMENT RESISTANCE IN PSYCHOTIC DISORDERS

The most widely used definition of treatment resistant schizophrenia (TRS) is based on "Kane criteria", from 1988 seminal study, which consists of: (1) at least three periods of treatment in the preceding 5 years with antipsychotic agents (from at least 2 chemical classes) at dosages equivalent to or greater than 1000 mg/day of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief, and (2) no period of good functioning (Kane et al. 1988). In majority of treatment guidelines, TRS is defined as a lack of response to at least two trials of antipsychotic agents, including at least on second-generation antipsychotic, in adequate dose over adequate period of time (ranging from 2 to 8 weeks) (ref). In the past, defining TRS was based primarily on the presence and severity of positive symptoms compared to the other aspects of the disorder such as cognitive impairments, social functioning and quality of life (Dold et al. 2014, Suzuki et al. 2012). In order to

address long-term therapy goal, i.e. recovery, Suzuki et al. recently proposed a definition of TRS that incorporates, in addition to Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric rating Scale (BPRS), several global measures (Global Assessment of Functioning (GAF), Clinical Global Impression (CGI) as well as Functional Assessment of Comprehensive Treatment of Schizophrenia (FACT-Sz) (Suzuki et al. 2012). All aforementioned scales are widely used worldwide, except FACT-Sz. This scale is added to the global assessment of TRS because it can offer more specific anchors for the global assessment of social functioning in patients with schizophrenia (Suzuki et al. 2012). However, this proposals needs to be tested in future trials.

EPIDEMIOLOGY

Prevalence of TRS differs based on the definitions and data-collection methods used in various studies. Early trials on the effects of antipsychotic treatment showed that approximately 30% of patients with schizophrenia had no response to treatment (Cane et al. 1996, Klein & Davis 1996), whereas in clinical trials conducted during the last decade of twentieth century 50 % of patients with schizophrenia responded adequately to antipsychotic medications (McEvoy et al. 1991, Kinon et al. 1993). Meta-analysis by Hegarty et al. based on 320 studies, which assessed the outcome of schizophrenia treatment studies conducted in the twentieth century, revealed that 20% of first-episode patients showed no response to antipsychotic medications following one year of treatment and only 50% of patients with chronic schizophrenia had positive outcome with antipsychotic therapy (Hegarty et al. 1994). These results revealed a shift towards poor outcomes in treatment of schizophrenia in recent decades.

MECHANISMS UNDERLYING TREATMENT RESISTANCE IN PSYCHOSIS

Efficacy of antipsychotic drug depends on its capacity to block dopamine D2 receptor (Howes et al. 2011). There is no medication proven to have antipsychotic efficacy without D2 binding affinity. Efficient drugs differs in their binding coefficients (sustained or transient) and there is also a difference in receptor occupancy and threshold for efficacy and side-effects (D2 striatal occupancy in range of 50-70-80%), but all these differences are still including D2 binding as the central mechanism. Therefore, it is logical that D2 occupancy examination is one of the most important targets in evaluating mechanisms underlying treatment resistance in psychosis.

The first neuroimaging data regarding antipsychotic non-response came from New York more than 25 years ago. Using (18F) N-methylspiroperidol and positron emission tomography, Wolkin et al. (1989) assessed dopamine receptor occupancy in 10 patients with schizophrenia before and after treatment with haloperidol. Responders and nonresponders had identical indices of (18F) N-methylspiroperidol uptake after treatment. The authors concluded that failure to respond clinically was not a function of neuroleptic uptake or binding in the CNS and suggested that D2 blockade is not guaranteeing therapeutic response.

On the other side, it was interesting to explore the possibility that subjects with no response to antipsychotic had more active dopaminergic transmission. The hypothesis was recently tested in London, where authors evaluated presynaptic dopamine synthesis capacity using ((18) F)-DOPA uptake positron emission tomography (PET), showing that subjects who responded to antipsychotics had elevated D-synthesis capacity than treatment-resistant cases or control subjects, particularly in associative and the limbic striatal regions. If schizophrenia subjects do not exhibit the elevation in dopamine synthesis capacity, feature that typically marks the disorder according to the Demjaha et al. (2012), antipsychotic treatment may be ineffective, thus reflecting a different underlying pathophysiology or a differential effect of antipsychotic treatment. This UK study was the first to provide direct evidence that dopamine synthesis was lower in treatment resistant cases, implicating once more that “one size not fits all”, thus supporting the Bleuler’s concept of Group of Schizophrenias (1911) and also the recent findings from Arnedo et al. (2015), intriguingly proofing that schizophrenia represents multiple genetically distinct disorders, instead of one disease.

The fact that TRS patients may represent a unique schizophrenia subpopulation, with peculiar clinical and neurobiological features was also supported by the recent findings from Italy, where authors compared smoker and non smoker therapy-resistant patients - TRS in terms of cognition, psychosis and social adjustment.

On the basis of cross-sectional study performed in Naples, authors suggested that tobacco smoking may represent an attempt to self-medicate in a sub – population of TRS patients with prominent negative symptoms, cognitive deficits, and poor social functioning (Iasevoli et al. 2013).

The first GWAS study of TRS was performed by Liou et al. (2012) in Han-Chinese population and included about 1300 participants (TRD patients and controls). Preliminary results revealed 19 SNPs with suggestive significant associations with TRS. Among the genetic loci with suggestive significance, NFKB1, RIPK4, and SLAMF1 were the most prominent, implicating that the NF-kappa B pathway may play an important role in the pathogenesis of TRS. The aforementioned pathway is regulating expression of many inflammatory factors, such as cytokines and adhesion molecules, so authors suggested that abnormal inflammatory response could lead to therapy-resistance in schizophrenia. In future, the association between cytokines and NF-kappa B in TRS remains to be established and replication of Liou et al. (2012) study is needed in worldwide population.

In summary, the literature is still sparse on TRS, but there is growing body of evidence suggesting that distinct molecular mechanisms operate in subjects who do not respond to antipsychotic drugs. Identifying the precise molecular pathway in TR cases is of high importance particularly in designing new drugs. Additionally, further evaluation of clozapine mechanism of action is urgent in better understanding of treatment – resistance enigma, as this drug is well known third-line medication which is efficient in many cases previously treated by different antipsychotics without success.

PHARMACOLOGICAL AND NON- PHARMACOLOGICAL INTERVENTIONS AGAINST TREATMENT RESISTANCE

Assessing pseudo-resistance

Before assuming treatment non-response, in case there is no adequate response to first antipsychotic drug, the following steps should be considered (assessing for “pseudo-resistance”): (a) re-evaluation of the diagnosis of a schizophrenia disorder (i.e. severe personality disorder as well as mania and depressive disorder in their acute phase; organic brain disorders such as brain tumors or encephalopathies), (b) ruling out comorbidities such as affective disorders, obsessive compulsive disorder and substance use disorders, (c) assessment of medication non-adherence by monitoring plasma levels or possibly using the long term injectable antipsychotic agents, since there is a evidence showing that more than 50 % of patients do not take their medication regularly (Goff et al. 2010), (d) checking if the sufficient dose with sufficiently long enough duration, as recommended by an international consensus survey (Gardner et al. 2010) of antipsychotic medication was achieved, (e) checking if the sufficient plasma levels of an anti-

psychotic drugs are achieved in order to exclude drug - drug interactions as well as antipsychotic agents metabolism abnormalities, (f) ruling out adverse effects since they can possibly mask a treatment response as they can mimic agitation or negative symptoms.

Strategies following non-response to first trial with an antipsychotic agent

If the clinical response is still not adequate despite addressing the above mentioned factors, two strategies, regarding the changes in patient's medication regimen are often considered in clinical practice, which include dose increase or switching the antipsychotic agent. Regarding the dose increase, all treatment guidelines state that increasing the dose of the antipsychotic drug above the officially approved dose is not recommended, except in the cases of fast metabolizers, confirmed by the genetic testing (Maric et al. 2014). Individual patients with polymorphism in the cytochrome P450 enzyme system which cause rapid elimination of drugs can benefit from high dose therapy (Maric et al. 2014). In contrast to high dose treatment, switching to another antipsychotic drug is a common used strategy in case of non-response to the first antipsychotic agent. Overall, evidence shows a slight advantage for switching the antipsychotic drug over high dose therapy in non-responders (Dold & Leucht 2014). When switching the antipsychotic drug, it is recommended that the first one should be discontinued gradually while simultaneously and gradually increasing the dose of the second one ("crossover titration") (Leucht et al. 2013). Also, alternative option is to maintain the dose of the first medication while increasing the dose of the second one gradually to a therapeutic level and then decrease the dose of the first drug ("overlap and taper") (Leucht et al. 2013). Preferably, an antipsychotic agent with a different receptor binding property should be administered (Englisch & Zink 2012).

TRS TREATMENT STRATEGIES

TRS treatment with clozapine

Pharmacotherapy with clozapine is currently classified as the first-line treatment in the treatment-resistant schizophrenia (Hasan et al. 2012, Lehman et al. 2010). Trial of clozapine is recommended only after at least two failed trials with two other different antipsychotic agents in adequate dosage (with plasma levels monitoring) during a minimum of eight weeks (Buchanan et al. 2009, Hasan et al. 2012, Lehman et al. 2010).

Various randomized trials have shown the efficacy of clozapine compared to other antipsychotic drugs in the treatment resistant patients (Souza et al. 2013, Essali et al. 2009). Early meta-analysis that included studies on TRS showed that only clozapine was significantly more efficacious than first generation antipsychotic agents (Chakos et al. 2001). Also, clozapine was superior in terms of efficacy compared to other second-generation antipsychotics in a phase II study of the Clinical Anti-

psychotic Trials of Intervention Effectiveness (CATIE trial) (McEvoy et al. 2006). In addition, a network meta-analysis including 212 randomized trials of 43 049 patients with schizophrenia with exclusion of trials on treatment resistant patients, clozapine had highest effect size in efficacy compared to other antipsychotic agents (Leucht et al. 2013). Recently, a systematic review and meta-analysis of 7 clinical trials with 648 patients with TRS showed that clozapine was more efficacious compared to olanzapine (Souza et al. 2013). Similarly, a meta-analysis comparing clozapine to risperidone in TRS patients found clozapine to be more efficacious, but in daily dose of at least 400 mg/day (Leucht et al. 2009).

Although clozapine is considered to be a gold standard TRS therapy, there are important limitations compared to other antipsychotic agents, i.e., 1% risk of agranulocytosis, slow dose titration and weekly blood counts monitoring during first 18 weeks of treatment and subsequently every month, as well as dose related lowering of seizure threshold (Hasan 2012, Buchanan 2010).

Finally, important TRS dimension is a risk of suicide. Clozapine is the only medication approved by US FDA to prevent suicide among patients with schizophrenia (Kasckow et al. 2011). Clozapine was first reported to reduce rates of suicidality in a study among 88 treatment-refractory patients with schizophrenia or schizoaffective disorder (Meltzer et al. 1995). In that trial, in the two years prior to initiation of clozapine therapy, 22 suicide attempts were reported, while in the 2 years after the start of clozapine treatment, the rate of suicide decreased by 88%. Also, the 2-year International Prevention Suicide Trial including 980 schizophrenia patients (260 of whom had TRS) showed that significantly lower rates of suicide behavior and suicide attempts in patients treated with clozapine than in those treated with olanzapine (Meltzer et al. 2003).

TRS treatment with other antipsychotic agents

Some treatment guidelines recommend therapy with olanzapine or risperidone, in case treatment of TRS with clozapine is not possible due to poor tolerance or occurrence of adverse effects (Hasan et al. 2012). Second generation antipsychotic such as risperidone, olanzapine and amisulpiride have also been shown in a large meta-analysis to have significant effect sizes, but these were mostly results from studies in non-resistant patients. However, in clinical trials including TRS patients, both olanzapine and risperidone had higher effect sizes than first generation antipsychotics (Leucht et al. 2013).

POLYPHARMACY IN TRS TREATMENT

Polypharmacy can be defined as the use of two medications of the same group such as antipsychotic medications (Divac et al. 2007), and its use in schizophrenia is widely spread and documented in our region, too (Divac et al. 2007, Jordanova et al. 2011, Maric et al. 2011). Given that approximately 30% of patients show

no adequate response to treatment with clozapine, their treatment is a challenge and pharmacologic or non-pharmacologic augmentation strategies remain the only option. Some authors suggest that combination treatment maybe effective in TRS (Lerner et al. 2004). In a meta-analysis that included 14 double-blind, randomized, placebo-controlled trials assessing combination of clozapine with second generation antipsychotic, there was a small but significant difference in favor of combination treatment compared to placebo (Taylor et al. 2012). However, combination of clozapine and second generation agents has been shown to be effective only in the randomized open studies and not in the double-blind trials (Barbui et al. 2009). The most investigated second generation agents in combination with clozapine is risperidone. Only one study supports the hypothesis that adding risperidone would improve resistant positive symptoms due to its strong affinity for D2 receptors (Josiassen et al. 2005). Furthermore, adding sulpiride to clozapine has been shown to be effective in improving positive and negative symptoms compared to placebo group (Shiloh et al. 1997). However, administering antipsychotic medication combination may be associated with significant metabolic side effects as well as treatment discontinuation (Gallego et al. 2012). In the large retrospective cohort study from Hungary, premature discontinuation was significantly more present in the combination than in the switching group (Katona et al. 2014).

Augmentation in TRS

Augmentation is defined as the simultaneous administration of the two medications of different classes. Many drugs (valproate, lithium, carbamazepine, beta-blockers, memantine, acetylcholinesterase inhibitors, selective serotonin uptake inhibitors, alpha 2-antagonists) have been tested in conjunction with antipsychotic agents in TRS (Leucht et al. 2013). No individual augmentation strategy has shown sufficient efficacy in TRS treatment. Augmentation strategies may be beneficial in case of targeting specific symptoms in TRS, i.e., antidepressants for comorbid depressive symptoms or negative symptoms; benzodiazepines for severe agitation (Dold et al. 2012, Singh et al. 2010).

Non-pharmacological augmentation strategies

Various guidelines recommend electroconvulsive therapy (ECT) as an augmentation strategy in clozapine non-responders, however only two studies provide evidence for its efficacy (Petrides et al. 2015, Kho et al. 2004).

Transcranial magnetic stimulation (rTMS) has been shown to significantly reduce negative symptoms in TRS (Dlabac-de Lange et al. 2010). However, longer term effects have not been investigated.

Psychosocial interventions

Although psychosocial interventions, if employed alone, are not sufficiently effective in TRS, providing them in conjunction with antipsychotic treatment have

been shown to improve patient outcome. These interventions include family psychoeducational interventions, social skills training, cognitive-behavioral treatment, assertive community treatment as well as crisis intervention (Pharoah et al. 2010, Kurtz et al. 2008, Wykes et al. 2008, Coldwell & Bender 2007, Joy et al. 2006).

CONCLUSIONS

In summary, therapy resistance patient is still a treatment challenge and to a large extent, strategies for such a patient are not covered by pharmacological guidelines. The evidence from randomized, controlled trials and meta-analysis, provides just a limited answer for the question: Is therapeutics resistance a trap for polypharmacy? We lack the main proof to conclude that treatment-resistance is the only predictor of polypharmacy and that polypharmacy, applied “de novo” that is as the first line of treatment of the specific disorder, is inefficient. But therapeutic guidelines recommend polypharmacy, especially in treatment resistant schizophrenia patients. Therefore we could conclude that polypharmacy is not a trap in psychiatry at this moment, but a necessity.

Acknowledgements:

We would like to thank Assoc. Prof. Nadja P. Maric, School of Medicine, University of Belgrade; dr Slobodanka Pejović-Nikolić, MD, MSci & dr Tijana Cvetić, PhD, Clinic for Psychiatry, Clinical Center of Serbia who provided a valuable contribution to manuscript preparation and the content.

Conflict of interest: None to declare.

References

1. Arnedo J, Svrakic DM, Del Val C, Romero-Zalaz R, Hernández-Cuervo H; Molecular Genetics of Schizophrenia Consortium, Fanous AH, Pato MT, Pato CN, de Erausquin GA, Cloninger CR, Zwir I: Uncovering the hidden risk architecture of the schizophrenias: confirmation in three independent genome-wide association studies. *Am J Psychiatry*. 2015; 172:139-153.
2. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W: Schizophrenia Patient Outcomes Research Team (PORT): The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull* 2010; 36:71–93.
3. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B: Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry* 2001; 158:518–526.
4. Cole JO, Goldberg SC, and Davis JM: Drugs in the treatment of psychosis: controlled studies. In: Solomon T, ed. *Psychiatric Drugs*. New York, NY: Gröllerand Stratton, 1966, pp153-180.

5. Coldwell CM, Bender WS: The effectiveness of assertive community treatment for homeless populations with severe mental illness: a meta-analysis. *Am J Psychiatry* 2007; 164:393.
6. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD: Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry*. 2012; 169:1203-1210.
7. Divac N, Jasović-Gašić M, Samardžić R, Lacković M, Prostran: Antipsychotic polypharmacy at the University Psychiatric Hospital in Serbia. *Pharmacoepidemiol Drug Saf* 2007; 16:1250-1251.
8. Dlabac-de Lange JJ, Knegtering R, Aleman A: Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: review and meta-analysis. *J Clin Psychiatry* 2010; 71:411.
9. Dold M, Li C, Tardy M, Khorsand V, Gillies D, Leucht S: Benzodiazepines for schizophrenia. *Cochrane Database Syst Rev* 2012; 11:CD006391.
10. Dold M & Leucht S: Pharmacotherapy of treatment-resistant schizophrenia: a clinical perspective. *Evid Based Ment Health* 2014; 17:33-37.
11. Englisch S & Zink M: Treatment-resistant Schizophrenia: Evidence-based Strategies. *Mens Sana Monogr* 2012; 10:20-32.
12. Essali A, Al-Haj Haasan N, Li C, Rathbone J: Clozapine versus typical neuroleptic medication for schizophrenia. *Cochrane Database Syst Rev* 2009; CD000059.
13. Gallego JA, Nielsen J, De Hert M, Kane JM, Correll CU: Safety and tolerability of antipsychotic polypharmacy. *Expert Opin Drug Saf* 2012; 11:527–542.
14. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ: International consensus study of antipsychotic dosing. *Am J Psychiatry* 2010; 167:686–693.
15. Goff DC, Hill M, Freudenreich O: Strategies for improving treatment adherence in schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2010; 71(Suppl 2):20–26.
16. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Thibaut F, Möller HJ; World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1 update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry* 2012; 13:318–78.
17. Hegarty JD, Baldessarini RJ, & Tohen M: One hundred years of schizophrenia: a meta-analysis of the outcome literature. *American Journal of Psychiatry* 1994; 151:1409-1416.
18. Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D, Valmaggia L, Allen P, Murray R, McGuire P: Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol Psychiatry* 2011; 16:885–886.
19. Iasevoli F, Balletta R, Gilardi V, Giordano S, de Bartolomeis A: Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. *Neuropsychiatr Dis Treat* 2013; 9:1113-1120.
20. Jordanova V, Maric NP, Alikaj V, Bajcs M, Cavic T, Iosub D, Mihai A, Szalontay A, Sartorius N: Prescribing practices in psychiatric hospitals in Eastern Europe. *Eur Psychiatry* 2011; 26:414-8.
21. Josiassen RC, Joseph A, Kohegyi E, Stokes S, Dadvand M, Paing WW, Shaughnessy RA: Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2005; 162:130-136.
22. Joy CB, Adams CE, Rice K: Crisis intervention for people with severe mental illnesses. *Cochrane Database Syst Rev* 2006; CD001087.
23. Kane J, Honigfeld G, Singer J, Meltzer H: Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988; 45:789–96.
24. Kasckow J, Felmet K, Zisook S: Managing suicide risk in patients with schizophrenia. *CNS Drugs* 2011; 25:129-143.
25. Katona L, Czobor P, Bitter I: Real-world effectiveness of antipsychotic monotherapy vs. Polypharmacy in schizophrenia: To switch or to combine? A nation wide study in Hungary. *Schizophr Res* 2014; 152:246–254.
26. Klein DF & Davis JM: *Diagnosis and Drug Treatment of Psychiatric Disorders*. Baltimore, Md: Williams & Wilkins, 1968.
27. Kinon BJ, Kane JM, John C: Treatment of neuroleptic resistant schizophrenia relapse. *Psychopharmacology Bulletin* 1993; 29:309-314.
28. Kho KH, Blansjaar BA, de Vries S, Babuskova D, Zwinderman AH, Linszen DH: Electroconvulsive therapy for the treatment of clozapine nonresponders suffering from schizophrenia - an open label study. *Eur Arch Psychiatry Clin Neurosci* 2004; 254:372-379.
29. Kurtz MM & Mueser KT: A meta-analysis of controlled research on social skills training for schizophrenia. *J Consult Clin Psychol* 2008; 76:491.
30. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J; American Psychiatric Association; Steering Committee on Practice Guidelines: Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004; 161(Suppl 2):1–56.
31. Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Asenjo Lobos C, Schwarz S, Davis JM: A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry* 2009; 166:152.
32. Leucht S, Cipriani A, Spinelli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; 382:951–962.
33. Leucht S, Heres S, Kissling W, Davis JM: Pharmacological treatment of schizophrenia. *Fortschr Neurol Psychiatr* 2013; 81:e1–13.
34. Levinson DF, Simpson GM, Sigh H: Fluphenazine dose, clinical response, and extrapyramidal symptoms during acute treatment. *Archives of General Psychiatry* 1990; 47:761-168.
35. Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, Kreyenbuhl J: Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry* 2004; 161(Suppl 2):1–56.
36. Liou YJ, Wang HH, Lee MT, Wang SC, Chiang HL, Chen CC, Lin CH, Chung MS, Kuo CC, Liao DL, Wu CK, Liu CM, Liu YL, Hwu HG, Lai IC, Tsai SJ, Chen CH, Liu HF, Chou YC, Chen CH, Chen YT, Hong CJ, Wu JY: Genome-wide association study of treatment refractory schizophrenia in Han Chinese. *PLoS One* 2012; 7.

37. Maric NP, Pavlovic Z, Jasovic-Gasic M: Changes in antipsychotic prescription practice at University Hospital in Belgrade, Serbia: 2009 vs.2004. *Acta Psychiatr Scand* 2011; 123:495.
38. McEvoy JP, Hogarty G, Steingard S: Optimal dose of neuroleptic in acute schizophrenia: a controlled study of the neuroleptic threshold and higher neuroleptic dose. *Archives of General Psychiatry* 1991; 48:739-745.
39. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, Swartz MS, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao J: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163:600–610.
40. Meltzer HY & Okayli G: Reduction of suicidality during clozapine treatment of neuroleptic resistant schizophrenia: impact on risk-benefit assessment. *Am J Psychiatry*. 1995; 152:183–190.
41. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S: International Suicide Prevention Trial Study Group: Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (Inter Se PT). *Arch Gen Psychiatry* 2003; 60:82–91.
42. Moskowitz A, Heim G: Eugen Bleuler's *Dementia praecox or the group of schizophrenias* (1911): a centenary appreciation and reconsideration. *Schizophr Bull* 2011; 37:471-479.
43. NICE: *Schizophrenia: full national guideline on core interventions in primary and secondary care*. National Institute for Clinical Excellence, 2003.
44. Lerner V, Libov I, Kotler M, Strous RD: Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; 28:89-98.
45. Petrides G, Malur C, Braga RJ, Bailine SH, Schooler NR, Malhotra AK, Kane JM, Sanghani S, Goldberg TE, John M, Mendelowitz A: Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *Am J Psychiatry* 2015; 172:52.
46. Pharoah F, Mari J, Rathbone J, Wong W: Family intervention for schizophrenia. *Cochrane Database Syst Rev* 2010; CD000088.
47. Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, Modai I, Khaikin M, Weizman A: Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *Br J Psychiatry* 1997; 171:569-573.
48. Singh SP, Singh V, Kar N, Chan K: Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry* 2010; 197:174–179.
49. Souza JS, Kayo M, Tassell I, Martins CB, Elkis H: Efficacy of olanzapine in comparison with clozapine for treatment-resistant schizophrenia: evidence from a systematic review and meta-analyses. *CNS Spectr* 2013; 18:82.
50. Suzuki T, Remington G, Mulsant BH, Rajji TK, Uchida H, Graff-Guerrero A, Mamo DC: Treatment resistant schizophrenia and response to antipsychotics: a review. *Schizophr Res* 2011; 133:54–62.
51. Suzuki T, Remington G, Mulsant BH, Uchida H, Rajji TK, Graff-Guerrero A, Mimura M, Mamo DC: Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. *Psychiatry Res* 2012; 197:1–6.
52. Taylor DM, Smith L, Gee SH, Nielsen J: Augmentation of clozapine with a second antipsychotic - a meta-analysis. *Acta Psychiatr Scand* 2012; 125:15–24.
53. Wolkin A, Barouche F, Wolf AP, Rotrosen J, Fowler JS, Shiue CY, Cooper TB, Brodie JD: Dopamine blockade and clinical response: evidence for two biological subgroups of schizophrenia. *Am J Psychiatry* 1989; 146:905-908.
54. Wykes T, Steel C, Everitt B, Tarrier N: Cognitive behavior therapy for schizophrenia: effect sizes, clinical models, and methodological rigor. *Schizophr Bull* 2008; 34:523.

Correspondence:

Jašović-Gašić Miroslava, MD, PhD
Neuropsychiatrist & Forensic psychiatrist
Faculty of Medicine, University of Belgrade
Djordja Vašingtona 19, 11000 Belgrade, Serbia
E-mail: profesorjasovicgasic@gmail.com