Psychiatria Danubina, 2021; Vol. 33, Suppl. 4 (part III), pp 1099-1105 *Conference paper*
Review

TREATMENT OF RESISTANT AND ULTRA RESISTANT SCHIZOPHRENIA

Antonija Medić[1], Dora Herceg[2] & Miroslav Herceg[2,3]
[1]*Institute of Emergency Medicine of Zagreb County, Croatia*
[2]*School of Medicine, University of Zagreb, Croatia*
[3]*University Psychiatric Hospital Vrapče, Zagreb, Croatia*

SUMMARY

Schizophrenia is a psychiatric disease which affects one percent of population. It is most common in young adults. It is primarily treated with typical and atypical antipsychotics. Resistant schizophrenia is a condition diagnosed after no response is noticed to two different antipsychotics of which one is atypical. The treatment has to be undertaken with adequate doses and duration of therapy. Clozapine is the golden standard in the treatment of therapy-resistant schizophrenia. It has shown its superiority among other antipsychotics in various studies. Aside from greater effectiveness, advantages include absence of extrapyramidal side effects. During clozapine treatment, regular blood tests should be performed as a screening method for agranulocytosis. Twenty to thirty percent od schizophrenia patients suffer from treatment resistant schizophrenia. Sixty percent of the latter ones show no therapeutic response to clozapine. In conclusion twelve to eighteen percent of all patients suffering from schizophrenia show no response to any form of treatment. Attempts to augment clozapine effectiveness are being made by increasing the dose of monotherapy, using antipsychotic polipharmacy or adding other types of drugs to clozapine. Unfortunately, these augmentation methods have not yet proven themselves to be effective enough to be added to standard therapy algorythms. On the other hand, electroconvulsive therapy is neuromodulatory method that shows promise in increasing therapeutic success. Although many methods of treatment are being researched, therapy-resistant schizophrenia remains a clinical challenge which affects a significant percentage of population and will require additional research.

Key words: *clozapine - electroconvulsive therapy - resistance schizophrenia - treatment*

* * * * *

INTRODUCTION

It is estimated that twenty to thirty percent of patients with schizophrenia suffer from TRS (Demjaha et al. 2017). Associations with this form of the disease are the length of the disease, poor functioning before disease development, drug abuse, a positive family history, and a lack of precipitating factors (Lindenmayer 2010). Numerous studies have investigated the therapeutic response in patients with schizophrenia, and different definitions of resistant schizophrenia have been offered by such research groups. A combination of data collected in different studies found that a patient could be considered to have TRS if he met the following criteria: no response to at least two antipsychotics (other than clozapine) at the appropriate dose and duration (four to six weeks), at least one of which was atypical. See evaluation of therapeutic response in Table 1 (Moore et al 2007). Patients lacking a response to clozapine and nonpharmacological treatment options such as electroconvulsive therapy form two subgroups of TRS. They are called clozapine resistant schizophrenia (ultraresistant) and ECT resistant schizophrenia (Howes et al. 2017). In terms of duration of therapy, recent data indicate that most of the therapeutic response occurs in the first two weeks of therapy. In the absence of a therapeutic response during this period, there is little chance that a response will occur later. This finding could lead to changes in the definition of TRS in the future (Samara et al. 2015). Possible confusion factors should be taken into account when diagnosing TRS. In some patients, it is not a resistant disease, but a lack of cooperation (Correll et al. 2011). To detect this type of confusion, doctors decided for injections of long-acting antipsychotics. In this way, the so-called "pseudo-resistance" is excluded (Kane et al. 2013). Another barrier to diagnosis is comorbid conditions, such as drug abuse (Lindenmayer 2010) or obsessive-compulsive disorder (Sa et al. 2009), which may contribute to the impression of poor antipsychotic efficacy (Lindenmayer 2010). In order to quantify the effect of antipsychotics, it is necessary to describe the criteria for response and remission. In doing so, we use scales to score the patient's symptoms at different stages of the therapeutic procedure and based on them we conclude about the success of the drug (Correll et al. 2011). Some of the scales used are:

- Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham 1987);
- Positive and Negative Syndrome Scale (PANSS) (Lally et al. 2016);
- Clinical Global Impression (CGI) (Leucht et al 2005);
- Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-SCZ) (Guy 1976);
- Global Assessment of Functions (GAF) (Tracy & Shergill 2014).

Table 1. Evaluation of therapeutic response (Moore et al. 2007)

Therapeutic response	
Complete	Change of 1 or 2 points on CGI scale or increase of ≥20 points on FACT-SCZ or decrease of ≥20% on BPRS/PANSS
Partial	Change of 3 points on CGI scale or increase of 10 to 20 points on FACT-SCZ/GAF scale or decrease of ≥10% on BPRS/PANSS
Resistance to therapy	
A	Documented therapeutic failure with 2 or more antipsychotics
B	Clearly documented therapeutic failure with one antipsychotic medication and a possibility of confirmation of therapeutic failure with other antipsychotic medication
C	Dose equivalent to ≥ 600 chlorpromazine per day lasting ≥ 6 weeks
D	No improvement on CGI scale ≥4 and on FACT-SCZ ≤49 or on GAF scale ≤50 points

Table 2. Criteria for ultra-resistant schizophrenia (Mouaffak et al. 2006)

Criterion	
Adequate dose	Plasma levels >350 ng/mL
Adequate period	8 weeks
No significant improvement	<20% decrease in patients on BPRS scale
Symptoms present	BPRS ≥45, on at least two of four positive symptoms on BPRS scale ≥4
Period of disease with patient's low-functioning	5 years

There are two different forms of therapeutic resistance. In a five-year prospective study involving 246 patients with the first episode of schizophrenia, 34 percent of patients were resistant to therapy (Lally et al. 2016). In that group, as many as 70 percent were resistant from the start. This form of resistance is called early therapeutic resistance. It is confirmed if there is no response to non-clozapine antipsychotic therapy within the first six months of schizophrenia without a period of remission. Other patients initially responded to therapy, but later developed resistance called late therapeutic resistance. It is confirmed if a new episode of the disease occurs after the therapeutic response in which there is no response to non-clozapine antipsychotics and the symptoms last longer than six months (Lally et al. 2016). Nor does clozapine treatment lead to success in all patients with TRS. Thirty to sixty percent of patients are thought to have a good response to clozapine, and a recent meta-analysis concludes that forty percent is the proportion of patients with satisfactory therapeutic outcomes. It follows that twelve to twenty percent of all patients diagnosed with schizophrenia will not be treated with either two antipsychotics or clozapine and they fall into the category of ultraresistant schizophrenia (Siskind et al. 2017). See criteria for ultra-resistant schizophrenia in Table 2.

The role of dopamine and glutamate in pathophysiology of treatment resistant schizophrenia

Role of dopamine

Despite the above evidence supporting the role of dopamine in the pathophysiology of schizophrenia, there are researches that calls this into question. One-third of patients do not improve their clinical picture with the use of antipsychotics (except clozapine), although a large number of receptors are occupied by the drug (Mortimer et al. 2010). Apart from antipsychotics, attempts to reduce the concentration of presynaptic dopamine do not lead to withdrawal of symptoms (Remington et al. 2012). From this, it can be concluded that in a significant number of patients the pathophysiological background is not related to dopamine dysfunction. One study also confirmed that there is no increase in dopamine levels in patients with resistant schizophrenia, and it is thought that another pathophysiological process lies in the background or the effect of antipsychotic therapy in these patients is different (Demjaha et al. 2012). Dopaminergic system plays an important role in antipsychotic response. Functional single nucleotide polymorphisms (SNPs) can change dopamine receptor expression or dopamine disposition and thus influence response to antipsychotic treatment (Terzić et al. 2016).

Role of glutamate

In the development of schizophrenia, the action of the neurotransmitter glutamate is also being investigated. It has an excitatory function and two types of receptors, metabotropic and ionotropic. One of the ionotropic receptors is NMDA, named N-methyl-D-aspartate, its own selective agonist, and its dysfunction is primarily investigated in the pathophysiology of schizophrenia (Kew & Kemp 2005). The hypothesis of an association between NMDA receptor dysfunction and schizophrenia arose from the observation that noncompetitive antagonists of the same, such as phencyclidine and ketamine, lead to immediate psychological effects similar to

those seen in schizophrenia (Javitt 2007). The overall mechanism of these symptoms is not fully elucidated, but is thought to be related to a decrease in the inhibitory role of GABA interneurons (Homayoun & Moghaddam 2007), resulting in increased pyramidal cell activation (Olney & Farber 1995). One meta-analysis describes a significant improvement and positive effect on residual positive or negative symptoms in patients taking antipsychotics and glutamatergic drugs (Tsai & Lin 2010). Of the imaging methods for investigating the effects and physiology of glutamate, one of the most commonly used methods is proton magnetic resonance spectroscopy (1H-MRS). With its help, glutamine and glutamate levels were measured in individuals with the first episode of the disease and in high-risk (Poels et al. 2014). In this way, higher levels of glutamine were recorded in the anterior cingulate cortex and nucleus caudatus (Marsman et al. 2013). There has been interest in using 1H-MRS in assessing future response to therapy because high levels of glutamate in the anterior cingulate cortex have been measured in patients with treatment-resistant schizophrenia (TRS) compared with patients responding to therapy. and with healthy controls (Poels et al. 2014).

Comparison of two neurotransmitters

Dopamine abnormalities are associated with psychotic symptoms, but their association with negative and cognitive symptoms is less clear (Javitt & Zukin 1991). Better knowledge of glutamate system dysfunction might be able to respond to ambiguities in patients with such symptoms. The function of dopamine neurons is regulated by glutamatergic projections in the dopamine nucleus in the midbrain (Miller & Abercrombie 1996). It has been previously explained that reduced availability or function of NMDA receptors acts on GABA neurons so that ultimately there is a decrease in inhibition in glutamatergic projections in the midbrain. This results in increased release of glutamate, and ultimately increased activetion of dopaminergic neurons. It can be assumed that dopamine abnormalities in schizophrenia arose secondarily, as a consequence of changes in the glutamatergic system (McGuire et al. 2008). Disorders can occur in both directions, so that abnormalities of one neurotransmitter lead to abnormalities in the functioning of the other. Although a number of questions from pathophysiology have not yet been answered, a better understanding of neurobiology should improve therapeutic options and create new treatment options (Howes et al. 2015, Šagud 2015).

TREATMENT OF THERAPEUTICALLY RESISTANT SCHIZOPHRENIA

Therapeutic options are currently limited and are divided into three groups: medications, neuromodulation methods, and psychotherapy.

Pharmacological options

Clozapine

Two large studies have confirmed the efficacy of clozapine. The first of these is CATIE (Clinical Antipsychotic Trial of Intervention and Effectiveness), which was supposed to compare the effects of newer antipsychotics with the typical antipsychotic perfenazine. The efficacy of all drugs tested except clozapine did not differ much. Clozapine has been shown to be superior to other drugs (Liebermann et al. 2005). Another study is CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study). Patients with TRS were randomized and received either clozapine or one of four selected atypical antipsychotics (risperidone, olanzapine, quetiapine, amisulpride) as therapy. Patients who received clozapine had a better quality of life, significant withdrawal of symptoms according to the PANSS scale during one-year follow-up, and improved overall mental health compared with patients receiving other drugs (Lewis et al. 2006). Regarding the comparison of clozapine with other antipsychotics, one of the meta-analyzes was conducted to compare the effects of fifteen different antipsychotics, typical and atypical, clozapine proved to be more effective than all other drugs studied (Leucht et al. 2013). The importance of clozapine in the treatment of TRS and the side effects that limit its clinical use are well known. The following study examined the efficacy and tolerability of antipsychotics in patients with TRS. Forty blind randomized studies involving 5,172 patients were analyzed in this study. Several significant differences were found in the outcomes of all studies. The most important finding of this study is that clozapine has not been shown to be significantly better than other drugs (Samara et al. 2016). In the end, we can conclude that clozapine is the most effective and gold standard drug for TRS (Bauchanan et al. 2010).

Strategies for enhancing therapeutic effect

As a first strategy and one way to enhance the effect of clozapine is to increase the dose. For most antipsychotics, doses close to the maximum effect have been determined, and it has been found that increasing the dose above these levels does not increase the clinical response or benefit of the drug, but increases the risk of side effects (Davis & Chen 2004). Several studies have investigated the efficacy of increasing antipsychotic doses in patients with a weak response to the standard dose. A meta-analysis involving five such studies concluded that there was no difference in the effects of standard and high doses and no improvement was achieved either on the scales of positive and negative symptoms or in the response rate. There is no evidence that increasing the dose of the drug would be more effective than the standard prescribed dose (Dold 2015). *The second strategy* that attempts to increase the effect

of treatment is a combination of two antipsychotics. A meta-analysis of sixteen studies found that the combination of two antipsychotics was more successful than continuous monotherapy, but this was confirmed only in smaller and lower quality studies. Negative symptoms decreased only in the aripiprazole group. Extensive research has not shown that the use of clozapine or a non-clozapine antipsychotic in combination with a second-generation antipsychotic would lead to improvement (Galling et al. 2017). Prescribing a combination of drugs is risky because it increases the chance of developing side effects. There is an increased risk of extrapyramidal symptoms, hyperprolactinaemia, sexual dysfunction, hypersalivation, sedation, cognitive impairment, and diabetes (Fleischacker & Uchida 2014). Evidence is not sufficient to use this method, even as a fourth or fifth step in a treatment algorithm (Pandurangi & Dalkilic 2008). *The third strategy* is to combine antipsychotics with other drugs, such as antidepressants, mood stabilizers, benzodiazepines, but so far the results have been disappointing (Thompson et al. 2016). *The fourth strategy* is the neuromodulation methods descrybed in the next section.

Methods of neuromodulation

These methods include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), transcranial direct current stimulation (tCDS), and vagus stimulation (VNS).

Electroconvulsive therapy is used as a second-line treatment for resistant schizophrenia, if there is no improvement in symptoms even with clozapine. About twelve ECT treatments are recommended at the same time as antipsychotics (Štrkalj Ivezić et al. 2001). One group of researchers analyzed twenty-six studies. Some of the conclusions were that ECT led to clinical improvement, patients were subsequently hospitalized for a shorter time, had a lower number of relapses compared to the placebo group. The combination of ECT and drugs showed only a slightly better effect than each of the options individually (Tharyan & Adams 2005). Another such study included data from eleven papers confirming the synergistic effect of a combination of ECT and antipsychotics, and by combining the two methods the effect of therapy could be seen more quickly. ECT has also been confirmed as an effective and safe method in the first episode of psychosis, especially if it is a resistant form (Maley et al. 2018). As a method of treatment it has its place in psychiatry and most modern guidelines recommend ECT as a method of treating resistant schizophrenia after clozapine (Grover et al. 2017). The combination of novel antipsychotics and ECT can be used safely and effectively in treatment-resistant schizophrenia (Ravanić et al. 2009).

Other neuromodulation methods

In the treatment of adult schizophrenia, the effects of TMS are studied in patients with positive symptoms, primarily auditory hallucinations, and from negative symptoms are focused on avolition, apathy, and cognitive difficulties. Research in this area cites the left temporoparietal cortex as a target area of the brain in the treatment of positive symptoms, and low frequencies are used in therapy. In patients with negative symptoms, the target area of application of TMS is the dorsolateral prefrontal cortex (Nieuwdrop et al.2015). TMS is a well-tolerated procedure with several absolute and relative contraindications (Narayana et al. 2015).

Deep brain stimulation is a neurosurgical method in which electrodes are inserted into the brain and a battery is placed in the chest area (Maley et al. 2018). The theoretical basis for the application of DBS in the treatment of schizophrenia are assumptions to a decrease in dopamine hyperactivity, and by targeting the nucleus accumbens, a balance of dopamine activity is expected (Cleary et al. 2015). The improvement of positive and negative symptoms has been described in a limited number of studies in the first phase (Gault et al. 2018). This method is invasive and some of the possible risks are intracranial hemorrhage and infections and similar conditions associated with invasive intracranial procedures (Schermer 2011).

Transcranial direct electricity current stimulation is a form of therapy in which a weak current is applied directly to the scalp that is sufficient to stimulate neuronal activity but not to induce depolarization (Palm et al. 2016). There are hypotheses that this approach could reduce negative symptoms by stimulating the left dorsolateral prefrontal cortex with the anode and reduce auditory hallucinations by stimulating the left temporoparietal joint with the cathode (Brunelin et al. 2012).

ECT is a method whose use is justified if there is no response to clozapine in patients with acute exacerbation of positive symptoms and catatonia. Other forms of neuromodulation are not officially methods of treating schizophrenia. The availability of data on their success is still limited and elucidating the therapeutic effects of these methods will present a challenge in future research (Maley et al. 2018).

TREATMENT OF ULTRARESISTANT SCHIZOPHRENIA

The concept of ultraresistant schizophrenia is relatively new. Other forms of treatment have been proposed as potential solutions, but few of them have shown success in previous research (Jakovljević 2015). One of the meta-analyzes included twenty-two randomized studies and investigated an increase in the effect of clozapine with concomitant administration of antiepi-

leptics in patients with resistant schizophrenia. The results showed that there was a significant improvement associated with both positive and negative symptoms in the case of topiramate and sodium valproate. Topiramate combination therapy often had to be discontinued due to the onset of side effects (Zheng et al. 2017). In addition to the above, topiramate and lamotrigine have been shown in a previous study to be superior to placebo in improving the treatment of positive and negative symptoms (Tiihonen et al. 2009). The findings of others studies show that, for example, glycine significantly worsened positive symptoms, and the effect on negative symptoms was no greater than placebo (Veerman et al. 2014). Although electroconvulsive therapy has been described in more detail in the previous text, it is important to emphasize one of the works within ultraresistant schizophrenia. The following study included five different studies, and the combined effect of clozapine and ECT led to improvement in over fifty percent of patients. Thus, ECT appears to be an effective and safe strategy to increase the effect of clozapine in TRS, but it is possible that in the case of the ultraresistant form, more ECT treatments will be required. As previously described, further research is needed in this area (Lally et al. 2016). Standardized diagnostic criteria for ultraresistant schizophrenia need to be established, with an emphasis on positive symptoms (Lee et al. 2016). Functional recovery should not be part of the criteria in the definition of ultraresistant schizophrenia, because clinical recovery characterized by the disappearance of positive symptoms is not necessarily confirmation of functional recovery (Lee et al. 2014).

CONCLUSION

The aim of this review was to define the therapy of resistant schizophrenia. The gold standard in treatment is clozapine, and the results of numerous studies have shown its superiority over both typical and atypical antipsychotics. The combination of clozapine and electroconvulsive therapy shows good results and most modern guidelines recommend this combination as a method of treatment after there is no improvement with clozapine. Despite this, some patients do not respond to any therapy. Research needs to be continued to find new treatments that will be more effective and have fewer side effects.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Antonija Medić & Dora Herceg contributed to the data collection, to the literature search and revised the manuscript for important intellectual content and substantially contributed to conception and design.

Antonija Medić, Dora Herceg & Miroslav Herceg substantial contributed to conception and design and making conclusions.

All of the authors critically reviewed the final draft of the manuscript and gave their final approval of the version to be published.

References

1. *Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF et al.: Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. Am J Psychiatry 2012; 169: 719–24*
2. *Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA et al.: The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull 2010; 36:71-93*
3. *Cleary D, Ozpinar A, Raslan A & Ko AL: Deep brain stimulation for psychiatric disorders: where we are now. Neurosurg Focus 2015; 38:1-24*
4. *Correll CU, Kishimoto T, Nielsen J & Kane JM: Quantifying clinical relevance in the treatment of schizophrenia. Clin Ther 2011; 33:16–39*
5. *Davis JM & Chen N: Dose response and dose equivalence of antipsychotics. J Clin Pssychopharmacol 2004; 24:192-208*
6. *Demjaha A, Lappin JM, Stahl D, Patel MX, MacCabe JH, Howes OD et al.: Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. Psychol Med 2017; 47:1981-9*
7. *Demjaha A, Murray RM, McGuire PK, Kapur S & Howes OD: Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry 2012; 169:1203-10*
8. *Dold M, Fugger G, Aigner M, Lanzenberger R & Kasper S: Dose escalation of antypsichotic drugs in schizophrenia: a meta-analysis if tandomized controlled trials. Schizophr Res 2015;166:187-93*
9. *Fleischacker WW & Uchida H: Critical review of antipsychotic polipharmacy in the treatment of schizophrenia. Int J Neuropsychopharmacol 2014; 17:1083-93*
10. *Galling B, Roldán A, Hagi K, Rietschel L, Walyzada F, Zheng W et al.: Antipsychotic augmentation vs. Monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World Psychiatry 2017; 16:77-89*
11. *Gault JM, Davis R, Cascella NG, Saks ER, Corripio-Collado I, Anderson WS et al.: Approaches to neuromodulation for schizophrenia. J Neurol Neurosurg Psychiatry 2018; 89:777–87*
12. *Grover S, Chakrabarti S, Kulhara P & Avasthi A: Clinical practice puidelines for management of schizophrenia. Indian J Psychiatry 2017; 59:19–33*

13. Guy W: ECDEU assessment manual for psychopharmacology. Rockville (MD): US Department of Health, Education and Welfare, 1976
14. Homayoun H & Moghaddam B: NMDA receptor hypofunction produces opposite effects on prefrontal cortex interneurons and pyramidal neurons. J Neurosci 2007; 27:11496–500
15. Howes O, McCutcheon R & Stone J: Glutamate and dopamine in schizophrenia: An update for the 21st century. J Psychopharmacol 2015; 29:97-115
16. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnhaum ML et al.: Treatment-resistant schizophrenia: Treatment response and resistance in psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. Am J Psychiatry 2017; 174:216–29
17. Jakovljevic M: Creative, person-centered and narrative psychopharmacotherapy or how to prevent and overcome treatment resistance in psychiatry. Psychiatr Danub 2015; 27:291-301
18. Javitt D & Zukin S: Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991; 148:1301–8
19. Javitt DC: Glutamate and schizophrenia: Phencyclidine, n-methyld-aspartate receptors, and dopamine-glutamate interactions. Int Rev Neurobiol 2007; 78:69–108
20. Kane JM, Kishimoto T & Correll CU: Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. World Psychiatry 2013; 12:216–26
21. Kay SR, Fiszbein A & Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–76
22. Kew JNC & Kemp JA: Ionotropic and metabotropic glutamate receptor structure and pharmacology. Psychopharmacol 2005; 179:4–29
23. Lally J, Ajnakina O, Di Forti M, Trotta A, Demjaha A, Kolliakou A et al.: Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first episode schizophrenia spectrum psychosis. Psychol Med 2016; 46:3231-40
24. Lally J, Gaughran F, Timms P & Curran SR: Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics. Pharmacogenomics Pers Med 2016; 9:117-29
25. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F & MacCabe JH: Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. Schisophr Res 2016; 171:219-24
26. Lee J, Takeuchi H, Fervaha G, Bhaloo A, Powell V & Remington G: Positive symptoms are associated with clinicians' global impression in treatment-resistant schizophrenia. J Clin Psychopharmacol 2014; 24:1622-9
27. Lee J, Takeuchi H, Fervaha G, Li Sin G, Foussias G, Agid O et al.: Subtyping schizophrenia by treatment response: antipsychotic development and the central role of positive symptoms. Can J Psychiatry 2016; 60:515-22
28. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F et al.: Comparative efficacy and tolerability of 15 antipsychotics in schizophrenia: a multiple treatment meta-analysis. Lancet 2013; 373:31-41
29. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E & Engel RR: What does the PANSS mean? Schizophr Res 2005; 79:231–8
30. Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP et al.: Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006; 32:715-23
31. Liebermann JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO et al.: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209-23
32. Lindenmayer JP: Long-acting injectable antipsychotics: focus on olanzapine pamoate. Neuropsychiatr Dis Treat 2010; 6:261-7
33. Maley CT, Becker JE & Shultz E: Electroconvulsive therapy and other neuromodulation techniques for the treatment of psychosis. Child Adolesc Psychiatric Clin N Am 2018; 18:1056-4993
34. Marsman A, van den Heuvel MP, Klomp DWJ, Kahn RS, Luijten PR & Hulshoff Pol HE: Glutamate in schizophrenia: A focused review and meta-analysis of 1H-MRS studies. Schizophr Bull 2013; 39:120–9
35. McGuire P, Howes OD, Stone J & Fusar-Poli P: Functional neuroimaging in schizophrenia: Diagnosis and drug discovery. Trends Pharmacol Sci 2008; 29:91–8
36. Miller DW & Abercrombie ED: Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. Brain Res Bull 1996; 40:57–62
37. Moore TA, Buchanan RW, Buckley PF, Chiles JA, Conley RR, Crismon ML et al.: The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry 2007; 68:1751–62
38. Mortimer A, Singh P, Shepherd C & Puthiryackal J: Clozapine for treatmentresistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. Clin Schizophr Relat Psychoses 2010; 4:49–55
39. Mouaffak F, Tranulis C, Gorevitch R, Poirier MF, Douki S, Olie JP et al.: Augmentation strategies of clozapine with antipsychotics in the treatment of ultraresistant schizophrenia. Clin Neuropharmacol 2006; 29:28-33
40. Narayana S, Papanicolaou AC, McGregor A, Boop FA & Wheless JW: Clinical applications of transcranialmagnetic stimulation in pediatric neurology. J Child Neurol 2015; 30:1111–24
41. Nieuwdorp W, Koops S, Somers M & Sommer IE: Transcranial magnetic stimulation, transcranial direct current stimulation and electroconvulsive therapy for medication resistant psychosis of schizophrenia. Curr Opin Psychiatry 2015; 28:222–8
42. Olney JW & Farber NB: Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995; 52:998–1007
43. Overall J & Gorham D: The brief psychiatric rating scale. Psychol Rep 1962; 10:799–812
44. Palm U, Segmiller F, Epple A, Freisleder FJ, Koutsouleris N, Schulte-Körne G et al.: Transcranial direct current stimulation in children and adolescents: a comprehensive review. J Neural Transm 2016; 123:1219–34
45. Pandurangi AK & Dalkilic A: Polypharmacy with second-generation antipsychotics: a review od evidence. J Psychiatr Pract 2008; 14:345-67
46. Poels EMP, Kegeles ls, Kantrowitz JT, Javitt DC, Liebermann JA, Abi-Dargham A et al.: Glutamatergic abnormalities in schizophrenia: A review of proton MRS findings. Schizophrenia Res 2014; 152:325-32

47. Ravanić DB, Pantović MM, Milovanović DR, Dukić-Dejanović S, Janjić V, Ignjatović DR, Jović SD, Jurisić V, Jevtović I: Long-term efficacy of electroconvulsive therapy combined with different antipsychotic drugs in previously resistant schizophrenia. Psychiatr Danub 2009; 21:179-86
48. Remington G, Kapur TS, Foussias G, Agid O, Mann S, Borlido C et al.: Tetrabenazine augmentation in treatment-resistant schizophrenia. J Clin Pharmacol 2012; 32:95–9
49. Sa AR, Hounie AG, Sampaio AS, Arrais J, Miguel EC & Elkis H: Obsessive-compulsive symptoms and disorder in patients with schizophrenia treated with clozapine or haloperidol. Compr Psychiatry 2009;50:437–42
50. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G et al.: Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. JAMA Psychiatry 2016; 73:199–210
51. Samara MT, Leucht C, Leeflang MM, Anghelescu IG, Chung YC, Crespo-Facorro B et al.: Early improvement as a predictor of later response to antipsychotics in schizophrenia: a diagnostic test review. Am J Psychiatry 2015; 172:617–29
52. Schermer M: Ethical issues in deep brain stimulation. Front Integr Neurosci 2011; 5:1–5
53. Siskind D, Siskind V & Kisely S: Clozapine response rates among people with treatment-resistant schizophrenia: data from systematic review and meta-analysis. Can J Psychiatry 2017; 62:772-7
54. Šagud M: Treatment-resistant schizophrenia: challenges and implications for clinical practice. Psychiatr Danub 2015; 27:319-26
55. Štrkalj Ivezić S, Folnegović Šmalc V, Mimica N, Bajs Bjegović M, Makarić G, Bagarić A et al.: Dijagnostičke i terapijske smjernice (algoritam) za liječenje shizofrenije. Preporuke Hrvatskog društva za kliničku psihijatriju Hrvatskog liječničkog zbora. Lijec vjesn 2001; 123:287-92
56. Terzić T, Kastelic M, Dolžan V, Plesničar BK: Genetic polymorphisms in dopaminergic system and treatment-resistant schizophrenia. Psychiatr Danub 2016; 28:127-31
57. Tharyan P & Adams CE: Electroconvulsive therapy for schizophrenia. Cochrane Database Syst Rev 2005; CD000076
58. Thompson JV, Clark JM, Legge SE, Kadra G, Downs J, Walters JT et al.: Antipsychotic polipharmacy and augmentation strategies prior to clozapine initiation: a historical cohort study of 310 adults with treatment-resistant schizophrenic disorders. J psychopharmacol 2016; 30:436-43
59. Tiihonen J, Wahlbeck K & Kivinemi V: The efficacy of lamotrigine in clozapine-resistant schizophrenia: a systematic review and meta-analysis. Schizophr Res 2009; 109:10-4
60. Tracy DK & Shergill S: Treatment-refractory schizophrenia: definition and assessment. In: Buckley PF, Gaughran F (edit.). Treatment-refractory schizophrenia-a clinical conundrum. Heildelberg (Germany): Springer, 2014; 1–19
61. Tsai GE & Lin P-Y: Strategies to enhance N-methyl-D-aspartate receptor-mediated neurotransmission in schizophrenia, a critical review and meta-analysis. Curr Pharm Des 2010; 16:522–37
62. Veerman SR, Schulte PF, Begemann MJ & De Haan L: Non-glutamatergic clozapine augmentation strategies: a review and meta-analysis. Pharmacopsychiatry 2014; 47:231-8
63. Zheng W, Xiang YT, Yang XH, Xiang YQ & De Leon J: Clozapine augmentation with antiepileptic drugs for treatment-resistant schizophrenia: A meta analysis of randomized controled trials. J Clin Psychiatry 2017; 78:498-505

Correspondence:
Ass. Prof. Miroslav Herceg, MD, PhD
University Psychiatric Hospital Vrapče
Bolnička c. 32, 10 000 Zagreb, Croatia
E-mail: miroslav.herceg@bolnica-vrapce.hr