

Editorial

Άρθρο σύνταξης

Treatment-resistant patients with schizophrenia

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The treatment of patients with schizophrenia who do not respond to antipsychotic therapy is clinically a major problem. Even after the introduction of second generation antipsychotics is estimated that approximately 20-30% of all patients with schizophrenia do not show clinical improvement with antipsychotic treatment and their clinical state is characterized by the presence of prominent serious and persistent positive symptoms.¹

These patients are considered as resistant to treatment. Although there are no officially consensus criteria for the concept of resistant to treatment patients, most studies² and treatment guidelines^{1,3-5} accept as operational criterion the "drug resistance", ie. the failure to achieve clinical improvement after administration of two different antipsychotics in sufficient doses and for a period 2–8 weeks. These criteria were initially proposed by Kane et al⁶ in the first study that demonstrated the superiority of clozapine versus chlorpromazine in the pharmaceutical treatment of patients with schizophrenia resistant to treatment.

Before a patient is diagnosed as resistant to treatment there must be excluded all the factors that affect the response to medication before. These factors include the reconfirmation of the diagnosis of schizophrenia, the exclusion of comorbidity with other mental disorder or substance abuse, severe side effects of treatment, administration of inadequate doses, insufficient duration of treatment, poor treatment compliance and pharmacodynamic factors. In case of the presence of any of the above factors therapeutic interventions should address for the elimination of them and measured concentration of plasma levels of the active agent is proposed.

When the diagnosis of resistance to treatment is established clozapine remains the first line therapeutic option and is recommended by the leading international treatment guidelines. Administration of clozapine in sufficient doses up to 300-850/900 mg per day for at least 3 to 6 months treatment is recommended, with gradual titration and weekly control of leukocytes for the first 18 weeks of treatment.

It is well established the superiority of clozapine in treatment-resistant patients with schizophrenia, but also for the treatment of patients with violent behavior or high risk of suicidality. Clozapine remains the only agent with these indications by the FDA since 1990. In a recent meta-analysis of 212 studies that included 43.049 patients clozapine achieved the highest effect size (effect size) in terms of antipsychotic efficacy and by a wide margin than other antipsychotics.⁷ Despite the documented effectiveness, clozapine is prescribed only in a small proportion of patients who meet the indications. Characteristically in the United States only a percentage of 2–3% treatment-resistant patients with schizophrenia are receiving clozapine.⁸

In case of non-response to clozapine is recommended either combination therapy, ie., the co-administration of a second antipsychotic or augmentation strategies, ie. co-administration with different classes drugs. Co-administration of clozapine with a second antipsychotic has become a routine clinical practice, although is not recommended by the treatment guidelines, since research data are limited and it is not supported by enough evidence. In a meta-analysis of 14 double-blind studies Taylor et al⁹ found a small, but statistically significant superiority in co-administration of clozapine with a second-generation antipsychotic compared to placebo. Sommer et al¹⁰ in their meta-analysis of 29 double-blind studies including studies with combination of antipsychotics and augmentation studies with other factors concluded that only the co-administration of clozapine with sulpiride was superior to placebo. They stated also that the evidence for co-administration of clozapine with another antipsychotic is minimal and insufficient. Barbui et al¹¹ in their meta-analysis showed a marginal superiority of co-administration of clozapine and a second antipsychotic in 10 open-label randomized trials, but not in 6 double blind placebo studies which showed no statistically significant difference. They concluded that from a clinical point of view the main message is that the prescription of a second antipsychotic has a little or even no advantage.

From the pharmacological point is more acceptable - logical a combination of an antipsychotic with low antidopaminergic properties, such as clozapine with a drug with strong affinity for dopamine receptors such as haloperidol, amisulpride, risperidone, sulpiride. For this reason, the most studied combination is that of co-administration of clozapine with risperidone.

Many drugs have been used as augmentation strategic with clozapine. These include lithium, valproate, benzodiazepines, antidepressants, lamotrigine, topiramate and experimental agents as agonists of NMDA receptors, D-5 fatty acids and antiinflammatories. For these agents there are insufficient data to support their efficacy in the treatment of psychotic symptoms in treatment-resistant patients on concomitant treatment with clozapine. Only Sommer et al¹⁰ reported evidence of superiority in co-administration clozapine and lamotrigine compared to placebo in two double-blind and three open randomized trials. Recent guidelines of World Federation of Societies of Biological Psychiatry¹ in their recommendations for augmentation strategies include with category of evidence B and recommendation grade 3 only the combination of clozapine and lamotrigine for treating treatment-resistant patients and the combination of clozapine and lithium for patients with additional emotional symptomatology but not for treatment-resistant patients.

Clozapine remains the reference drug for the treatment of resistant patients with schizophrenia. The resistance to treatment today still directly related to the presence of positive symptoms, although our long-term therapeutic goals for schizophrenia included today even the pursuit of recovery. In addition areas such as social and cognitive functioning and quality of life parameters are not included in the definition of treatment-resistant schizophrenia. For this reason, many researchers argue that is required a broader approach and definition of the concept of "resistance to treatment".¹²

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