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Oral presentation

A critical evaluation of antipsychotics; towards the next generation?

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Antipsychotic drugs have been used for more than 50 years in the management of psychotic symptomatology. The dopamine-2 receptor (D2) antagonistic properties of conventional antipsychotics, as probably the mechanism of their action, formulated the dopamine hypothesis of schizophrenia. This hypothesis is now revised, since beyond the overactivation of dopaminergic systems in mesolimbic dopamine pathway leading to the positive symptoms, there is also evidence of hypodopaminergic activity in the mesocortical dopamine pathway related to the negative symptoms and cognitive impairment.

In the clinical practice, it has been observed that approximately one-fifth of patients do not respond to neuroleptic drugs, even when there are high levels of D2 receptor occupancy. Thus, with the progress in psychopharmacology and the discovery that clozapine, an atypical antipsychotic, binds to multiple receptors – other than D2 receptors – and the identification that serotoninergic and other neurotransmitter systems are involved in the pathophysiology and symptomatology of the disease, new compounds have been isolated. More recently, the partial agonistic activity at both D2 and serotonin receptors has added a novel pharmacological treatment approach.

Atypical antipsychotic drugs have been developed with multimodal mechanisms of action. These second generation antipsychotics have an increased therapeutic effect on a broader spectrum of symptomatology, including the positive and also the negative symptoms, combine efficacy with good tolerability, and result in a better quality of life and improved compliance. Switching to atypicals can be associated with enhanced response rates. The use of these compounds is now considered as first-line treatment not only for patients with first episode psychosis, but also in the long-term management of the disease. Among them, important differences exist regarding their potential to cause metabolic abnormalities and weight gain.

Schizophrenia is a complex disease with high heterogeneity and multiformity in its clinical expression. The choice of the pharmacological treatment should be based on the existing guidelines, as well as on the balance of the risks and benefits to the individual patient.