

## ANTIPSYCHOTICS - HISTORY OF DEVELOPMENT AND FIELD OF INDICATION, NEW WINE - OLD GLASSES

Miroslava Jašović-Gašić<sup>1,2</sup>, Olivera Vuković<sup>1,3</sup>, Maja Pantović<sup>3</sup>,  
Tijana Cvetić<sup>3</sup> & Nadja Marić-Bojović<sup>1,3</sup>

<sup>1</sup>Faculty of Medicine, University of Belgrade, Belgrade, Serbia

<sup>2</sup>Academy of Medical Science, Serbian Medical Society, Belgrade, Serbia

<sup>3</sup>Clinic for Psychiatry, Clinical Center of Serbia, Belgrade, Serbia

### SUMMARY

More than half a century ago, Delay and colleagues have discovered, quite accidentally, that antihistamine (chlorpromazine) relieves psychotic symptoms. This discovery prompted further investigation through a series of performed experiments aimed to elucidate the antipsychotic mechanism of action. Initial results have shown that antipsychotic drugs in experimental animals lead to "neuroleptic effect" (indifference). However, not until the end of 1960s, it becomes clear that all previously known antipsychotics, block dopamine receptors, particularly postsynaptic D<sub>2</sub> receptors. The next three decades marked the development and application of these so-called classic neuroleptics in the treatment of psychotic patients. During the nineteen nineties, as a result of ongoing efforts to achieve greater efficiency and reduce the scope of side effects, novel antipsychotics were synthesized (second generation antipsychotics - SGA). As a result the notion of serotonin-dopamine antagonist (SDA) was formulated. According to one of the hypothesis, "new", so called atypical antipsychotic drugs strongly block the serotonin (5-HT<sub>2</sub>), and weakly block the dopamine (D<sub>2</sub>) receptors. Yet, there is still a debate as to the molecular basis of atypicality, whether it is in dopaminergic and serotonergic antagonism of neurotransmission or it lays exclusively in the modulation of dopaminergic system and dissociation rate at the level of D<sub>2</sub> receptors in specific brain regions.

Although the synthesis and use of antipsychotics in clinical practice have radically changed not only the basic approach to the patient, but also the quality of life of millions of people, the question remains whether this is just "old wine in new glasses".

**Key words:** antipsychotics – history - indication

\* \* \* \* \*

### INTRODUCTION

More than half a century ago, Delay and colleagues have discovered, quite accidentally, that antihistamine (chlorpromazine) relieves psychotic symptoms. This discovery prompted further investigation through a series of performed experiments aimed to elucidate the antipsychotic mechanism of action. Initial results have shown that antipsychotic drugs in experimental animals lead to "neuroleptic effect" (indifference). However, not until the end of 1960s, it becomes clear that all previously known antipsychotics, block dopamine receptors, particularly postsynaptic dopamine (D<sub>2</sub>) receptors. The next three decades marked the development and application of these so-called classic neuroleptics in the treatment of psychotic patients. During the nineteen nineties, as a result of ongoing efforts to achieve greater efficiency and reduce the scope of side effects, novel antipsychotics were synthesized (second generation antipsychotics - SGA). As a result the notion of serotonin-dopamine antagonist (SDA) was formulated. According to one of the hypothesis, "new", so called atypical antipsychotic drugs strongly block the serotonin (5-HT<sub>2</sub>), and weakly block the dopamine (D<sub>2</sub>) receptors. Yet, there is still a debate as to the molecular basis of atypicality, whether it is in dopaminergic and serotonergic antagonism of neurotransmission or it lays exclusively in the modulation of dopaminergic system and dissociation rate at the level of D<sub>2</sub> receptors in specific brain regions.

However, the synthesis and use of antipsychotics in clinical practice have radically changed not only the basic approach to the patient, but also the quality of life of millions of people.

### PHARMACOLOGICAL FEATURES OF SOME ANTIPSYCHOTIC DRUGS

Identifying the most important pharmacological features of some antipsychotic drugs makes their pharmacological classification relevant. So, we distinguish between predominantly anti-dopaminergic antipsychotics that can be selective and non selective and predominantly non-dopaminergic antipsychotics that can be divided into so-called SDA (serotonin-dopamine antagonists) antipsychotics and MARTA (Multiple Antagonized Receptors Targeted Antipsychotics) antipsychotics. New antipsychotics are expected to have potent antipsychotic effect, effect on the broader range of schizophrenic symptoms, including the effect on the positive – productive and on the negative - deficit symptoms of schizophrenia, the narrow receptor profile (so-called "clean antipsychotics"), and not to cause early and late extrapyramidal effects, and other known side effects (e.g. cardio-and hepatotoxicity, proconvulsive effects, hyperprolactinemia, weight gain, neuroleptic malignant syndrome). So far we have no ideal antipsychotic that would meet all these expectations, but several new second-generation antipsychotics represent significant progress in this regard.

## **SECOND GENERATION ANTIPSYCHOTICS (SGA) - ATYPICAL ANTIPSYCHOTICS**

Second generation antipsychotics (SGA) or "atypical" (clozapine, risperidone, olanzapine and others) have been increasingly introduced into the clinical practice, over the last 15 years. In the course of our long-time work in the treatment of patients with schizophrenia, we focused on studying efficacy and tolerability of antipsychotic therapy, particularly of the SGA (Jašović-Gašić & Marić 2004). Numerous studies we conducted have confirmed the efficacy of SGA in the treatment of positive and negative symptoms of schizophrenia, and some clusters of symptoms (disorganized thinking, aggression, hostility, anxiety, and depression) present in the patients with schizophrenia.

The studies indicate that the antipsychotic use increased over the last decades, shifting from FGA to SGA. Atypical antipsychotics have revolutionized the treatment of schizophrenia, becoming the treatment of choice for patients not only during their first episode, but also throughout their life course. Furthermore, SGA are widely used for the treatment of a broad range of symptoms and disorders, both in psychiatry and somatic medicine. The use of typical antipsychotics in general declined, but is still frequent in schizophrenia. In contrast, the use of atypical agents over the last decades expanded for bipolar affective disorder, remained stable for depression, and declined for schizophrenia. Overall, the use of SGA for indications where FDA approval and associated clinical evidence is less certain increased. However, the value of innovation, the benefits of widening atypical antipsychotic use should be weighed against a number of clinical and social factors (Jašović-Gašić et al. 1997, Weiss et al. 2000).

## **DEPRESSION IN SCHIZOPHRENIA**

In our project "Depression in schizophrenia," we are particularly dealt with the fact that the depressive symptoms are frequently seen in patients with schizophrenia, as part of the disease itself or as its separate phase. The presence of depressive symptoms complicates the course of the disease, affecting not only the morbidity, mortality, but also increasing the number of suicides in this population of patients. The prevalence of depressive disorders varies, depending on the approach applied, from 7% to 79%! In particular, we would like to highlight our long-time research on the use of first atypical antipsychotic, clozapine, which have demonstrated its efficacy in treating depressive syndrome in schizophrenia (Alexander et al. 2011), and superiority to antidepressants (Jašović-Gašić et al. 1997), as well as significant efficacy in reducing aggression and impulsivity in psychotic patients (Jašović-Gašić et al. 1998). Within several long-term follow-up studies we have also shown favorable effects of clozapine applied in maintenance therapy in patients with chronic form of

schizophrenia, in the therapy-resistant cases of the disorder, as well as its efficacy in the treatment of negative syndrome in schizophrenia (Paunović et al. 1988, Marinković et al. 2000).

## **THE NEW FORMULATIONS OF SECOND GENERATION ANTIPSYCHOTICS**

Taking into account various factors that influence the adherence of patients in treatment, we conducted numerous multi-center studies in which we have paid special attention to new formulations of atypical antipsychotics (solution, long-lasting inject-able form), as well as attitudes and patient satisfaction with therapy (Jašović-Gašić et al. 2005). We have shown that switching the therapy of clinically stable patients on classical or atypical oral antipsychotics or depot form to the first long-lasting inject-able second-generation antipsychotic may lead to further improvement of efficiency and lead to reduction of side effects. Long-term use of this form of medication leads to fewer hospitalizations and length of hospital stay, therefore significantly reducing total cost of treatment. These forms of medication are indicated for treatment of non-compliant patients, patients with first psychotic episode, young patients, and with patients who while receiving depo form of first generation antipsychotic medication had serious side-effects.

## **THE NEUROENDOCRINE AND METABOLIC CHANGES ASSOCIATED WITH THE IMPLEMENTATION OF SECOND GENERATION ANTIPSYCHOTICS**

Second generation antipsychotics have a negative characteristic to induce weight gain and cause changes in glucose and lipid metabolism. Despite the fact that the increase in body weight on SGA reaches a plateau after a certain time, their application can cause very serious consequences. In literature we can find some cases of patients with weight gain of 50 pounds after five years of use these medications. Considering the data on the increasing prevalence of metabolic syndrome associated with the implementation of second generation antipsychotics, we investigated the neuroendocrine and metabolic changes in schizophrenic patients with normal body weight (Popović et al. 2007).

We have published several papers, different methodological designs, from case studies, across-sectional study to the longitudinal study. One of the first works was a case report of a patient who, after four months of therapy with SGA gained 20 kg in weight (Doknić et al. 2007). There is growing evidence that peripheral hormones, leptin from adipose tissue, insulin from the pancreas, and ghrelin from the stomach, together with central signals modulate the activity of hypothalamic

orexigenic and anorexigenic peptidergic neurons in the hypothalamus. In the hypothalamus, serotonin and histamine integrate signals from the peripheral action of hormones in order to provide precise control of nutritional status. SGA act through many receptors, including serotonin (5HT<sub>2</sub> and 5HT<sub>2c</sub>) and histamine, reducing their impact through anorexigenic signals (serotonin, histamine, leptin). In this regard, we recently conducted the first study that shows a consistent increase in prolactin levels and the long effect of leptin in the application of SGA to natural conditions. However, it remains an open question whether the pharmacokinetic and pharmacodynamic advantages of this formulation in relation to oral, are associated with favorable metabolic and neuroendocrine profiles (Jašović-Gašić et al. 2010).

## CLINICAL GUIDELINES AND TREATMENT ALGORITHMS

Algorithm (guide, guidelines) provides concise recommendations on diagnosing and treating various mental disorders. The need for the introduction of clinical guidelines and treatment algorithms to clinical practice is consistent with the significant improvement of scientific knowledge in the field of pharmacotherapy in the last few decades and the consequent development of new therapeutic options. We are aware of the need for the existence of national therapeutic guidelines harmonized with current knowledge; we have collaborated in the projects of the Serbian Medical Society and the Medical Faculty in Belgrade to develop guidelines for the treatment of schizophrenia, bipolar affective disorder and depression. Recent study conducted at Clinic for Psychiatry Clinical Center showed that about 65% of psychiatrists apply the relevant national or international therapeutic guidelines in their clinical practice, demonstrating the importance of algorithms in the unification and rationalization of work (Divac et al. 2009).

## CONCLUSIONS

Although the synthesis and use of antipsychotics in clinical practice have radically changed not only the basic approach to the patient, but also the quality of life of millions of people, the question remains whether this is just "old wine in new glasses." However, today, at the beginning of the new millennium, psychiatry, according to a variety of effective treatments, at least when it comes to antipsychotic therapy is one of the richest fields of medicine.

### Correspondence:

Miroslava Jašović-Gašić, MD, PhD, Neuropsychiatrist & Forensic psychiatrist  
Professor of Faculty of Medicine, University of Belgrade  
Associate Member of Academy of Medical Science, Serbian Medical Society  
Djordža Vašingtona 19 or Bulevar Despota Stefana 7, 11000 Belgrade, Serbia  
E-mail: mjasovicgasic0@gmail.com

**Acknowledgements:** None.

**Conflict of interest:** None to declare.

## REFERENCES

1. Alexander GC, Gallagher SA, Mascola A et al. Increasing off-label use of antipsychotic medications in the United States, 1995–2008. *Pharmacoepidemiology and Drug Safety* (2011) DOI: 10.1002/pds
2. Divac N, Maric NP, Damjanovic A et al. Use or underuse of therapeutic guidelines in psychiatry? *Psychiatr Danub* 2009; 21:224-9.
3. Doknić M, Marić N, Damjanović A et al. Uloga antipsihotika u promeni telesne težine i metaboličkog statusa. *Acta Clinica* 2007; 7:173-179.
4. Jasovic-Gasic M, Maric N, Doknic M et al. Metabolic and neuroendocrine effects of long-acting injectable risperidone in real-life conditions. *Eur Psychiatr* 2010; 25 (Suppl 1): P03-341
5. Jasovic-Gasic M, Maric N. Risperidon vs. other antipsychotics in schizophrenia: The assesment of patient attitudes. *Psychiatr Danub* 2004; 16:127-31.
6. Jasovic-Gasic M, Crnobaric C, Miljevic C et al. Clozapine in the treatment of depressive syndrome in schizophrenia. *Biol Psychiatry* 1997; 42(Suppl 1): 170S.
7. Jasovic-Gasic M, Miljevic C, Crnobaric C. Antidepressants versus clozapine in the treatment of depressive syndrome in schizophrenia. *Eur Neuropsychopharmacol* 1997; 7(Suppl 2): S272.
8. Jasovic-Gasic M, Crnobaric C, Miljevic C et al. Efficacy of Clozapine therapy in aggression. *Eur Psychiatry* 1998; 13(Suppl 4): 314S.
9. Paunovic RV, Jasovic-Gasic M, Bogdanovic M et al. Clozapine in the treatment of negative symptoms in schizophrenia. *Ibid* 1, *Psychopharmacology* 1988; Suppl. to Vol 96:344.
10. Jasovic-Gasic M, Maric N, Damjanovic A. Risperidone liquid in psychotic disorders—efficacy and attitudes. *Psychiatr Danub* 2005; 17:191-6.
11. Marinkovic D, Totic S, Jasovic-Gasic M et al. Clozapine is efficient in long term treatment of negative syndrome, but no cognitive functioning, in schizophrenia? A three-year follow-up study. *Eur Neuropsychopharmacol* 2000; 10(Suppl 3): 321.
12. Popovic V, Doknic M, Maric N et al. Changes in Neuroendocrine and Metabolic Hormones Induced by Atypical Antipsychotics in Normal-Weight Patients with Schizophrenia. *Neuroendocrinology* 2007; 85:249-56.
13. Weiss E, Hummer M, Koller D et al. Off-label use of antipsychotic drugs. *J Clin Psychopharmacol* 2000; 20:695-8.