

Brilaroxazine

The current psychopharmacological treatment of schizophrenia, which involves both typical and atypical antipsychotics, is often cumbersome in terms of tolerance difficulties. Those occur because of frequent side effects that lead to limited adherence and effectiveness. Furthermore, antipsychotics do not provide a wide range of efficacy in different symptom classes so it is no surprise that up to 30 % of patients are refractory to the current treatment. This leads to the conclusion that critical necessities are often unmet in treatment of schizophrenia.

Brilaroxazine (RP5063, also known as RP5000) is an atypical antipsychotic in research and development under the auspices of Reviva Pharmaceuticals. It is considered to be a modulator of the dopamine-serotonin system, which has a pronounced affinity for a number of receptors of the serotonin and dopamine system. It is structurally similar to cariprazine, brexpiprazole, and in particular to aripiprazole. Studies have shown that it has a high affinity for $D_{2/3/4}$ and $5-HT_{1A/2A/2B/2C/6/7}$ receptors and a moderate affinity for the serotonin transporter.

It demonstrated activity of a partial agonist on dopamine D_2 , D_3 , D_4 receptors, and serotonin $5-HT_{1A}$ and $5-HT_{2A}$ receptors with antagonistic activity on serotonin $5-HT_{2B}$, $5-HT_6$ and $5-HT_7$ receptors. Initial clinical experience in healthy volunteers and patients with schizophrenia and schizoaffective disorder define this molecule as a promising addition to current psychopharmacological modalities. Pharmacokinetics of brilaroxazine proved to be very predictable and consistent. We would emphasize its relatively rapid oral absorption, linear, dose-dependent increase in maximum concentration, lack of excess accumulation and long half-life of over 40 hours, which altogether lead to simple dosing and administration once a day. It is believed that the balance between antagonism and agonism on the dopamine and serotonin system underlies its stabilizing effect and contributes to the lower incidence of side effects related to the use of already available antipsychotics. During Phase I and II of clinical trials, it did not cause cardiometabolic, cardiovascular, neurological, or endocrinological side effects that would complicate ongoing treatment. Brilaroxazine has so far proven effective in studies of patients with acute-phase schizophrenia. Namely, during placebo-controlled

phase II of clinical trials it showed significance when compared to placebo in the total PANSS score on day 28 matched to baseline. It was also investigated in animal models of psychosis and episodic memory in mice and had a significant effect on subchronic phenylcyclidine-induced damage of novel objects recognition which is used as a correlate of episodic memory, but did not affect reverse learning which is used as a correlate of executive functions. Its administration significantly increases the release of cortical dopamine, which may be crucial for some of its pro-cognitive properties. These results indicate that brilaroxazine, alone or as an adjunct treatment, has multiple bases for improving some of the cognitive deficits associated with schizophrenia. The molecule is currently in phase III of clinical trials as a potential drug for the treatment of schizophrenia and is also being investigated as treatment for bipolar affective disorder, major depressive episode, psychosis/agitation in Alzheimer's dementia, psychotic conditions in Parkinson's disease, attention deficit and hyperactivity disorder and autism.

In regard to indications outside the domain of psychiatric and neurological diseases, brilaroxazine has demonstrated the potential for treatment of pulmonary arterial hyper-

tension and idiopathic pulmonary fibrosis. There is evidence that it prevents monocrotaline-induced pulmonary hypertension in rats, which can be explained by the fact that regulation of serotonin 5-HT_{2A} and 5-HT_{2B} receptors is impaired in the pulmonary arterial hypertension, a disease characterized by remodeling and constriction of the pulmonary vasculature. An attempt was made to prove the benefits of the molecule using the above animal model, and it was found that it reduces pulmonary vascular pathology and optimizes hemodynamics by acting on right ventricular pressure, right ventricular hypertrophy, saturation of systemic blood with oxygen, and overall rat health. Also, the drug has shown strong efficacy in highly investigated translational animal models that have been shown to mimic pulmonary fibrosis in humans, significantly improving survival rates and reducing concentration of inflammatory cytokines and lung fibrosis. The US Food and Drug Administration has awarded it the status of the so-called orphan drug for these diseases, given its potential for clinically significant improvement and stabilization of pulmonary function.

*Assistant Professor Vjekoslav Peitl, MD, PhD
Deputy Editor
Darko Vlabović, MD*

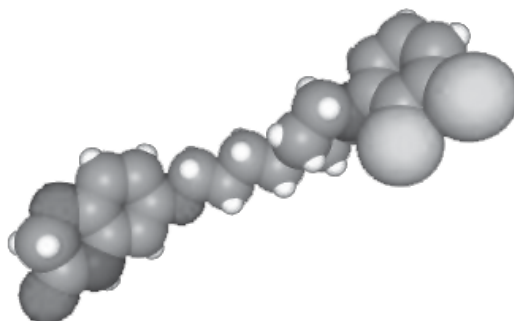


Figure 1. Three-dimensional chemical structure of brilaroxazine.

References

1. Stahl SM. *Stahlovi temelji psihofarmakologije*. Jastrebarsko: Naklada Slap; 2017.
2. Karlović D, Peitl V, Silić A. *Shizofrenije*. Klinički bolnički centar Sestre milosrdnice: Naklada Slap; 2019.
3. Bhat L, Cantillon M, Ings R. Brilaroxazine (RP5063) Clinical Experience in Schizophrenia: A New Option to Address Unmet Needs. *J Neurol Neuromedicine*. 2018;3:39-50.
4. Cantillon M, Ings R, Prakash A, Bhat L. A Population Pharmacokinetic and Pharmacodynamic Analysis of RP5063 Phase 2 Study Data in Patients with Schizophrenia or Schizoaffective Disorder. *Eur J Drug Metab Pharmacokinet*. 2018;43:573-585.
5. Cantillon M, Prakash A, Alexander A, Ings R, Sweitzer D, Bhat L. Dopamine serotonin stabilizer RP5063: A randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophrenia Research*. 2017;189:126-133.
6. Bhat L, Hawkinson J, Cantillon M, Reddy DG, Bhat SR, Laurent CE, et al. RP5063, a novel, multimodal, serotonin receptor modulator, prevents monocrotaline-induced pulmonary arterial hypertension in rats. *Eur J Pharmacol*. 2017;810:92-99.
7. Rajagopal L, Kwon S, Huang M, Michael E, Bhat L, Cantillon M, et al. RP5063, an atypical antipsychotic drug with a unique pharmacologic profile, improves declarative memory and psychosis in mouse models of schizophrenia. *Behav Brain Res*. 2017;332:180-199.
8. Drugbank database (cited September 21th 2019.) Available from: <https://www.drugbank.ca/drugs/DB09226>
9. MD Magazine. (cited September 28th 2019). Available from: <https://www.mdmag.com/medical-news/fda-grants-reviva-pharmaceuticals-rp5063-orphan-designation-for-ipf>

