Disappointing outcome of bitopertin treatment for negative symptoms in schizophrenia
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Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

Two new phase III clinical trials investigating the efficacy and safety of bitopertin, a glycine uptake inhibitor considered to be a promising new add-on therapy for treating negative symptoms in schizophrenia, failed to show a benefit of the drug over placebo. The findings throw a wrench in the hopeful efforts to find a treatment for negative symptoms of schizophrenia, which account for some of the most debilitating aspects of the disorder and are associated with poorer outcomes in patients.

The outcomes of the trials were published in a paper in Biological Psychiatry by Dr. Dragana Bugarski-Kirola of Roche Pharmaceuticals in Basel, Switzerland. The randomized, double-blind, parallel-group, placebo-controlled studies were a collaboration between Roche and several research institutions around the world.

"We are back to the drawing board," said Dr. John Krystal, Editor of Biological Psychiatry.

Previous attempts to treat negative symptoms have employed drugs, hormones, and brain stimulation, but none have provided the desired clinical benefit. Research pointing at glutamate signaling in negative symptoms has spurred the idea of targeting glutamate receptors, but this approach has failed in large trials. Glycine reuptake inhibitors have been considered a promising alternative to enhance glutamatergic signaling, and a small proof-of-concept study showed that bitopertin, which selectively inhibits glycine transporter type 1 (GlyT-1), reduced negative symptoms in stable patients with schizophrenia.

"GlyT-1 inhibition was one of the most promising approaches to the treatment of schizophrenia," said Krystal. "While it still may be possible to optimize GlyT-1 inhibition as a treatment, these negative results suggest GlyT-1 inhibition is not a broadly effective or optimal therapeutic strategy to enhance NMDA glutamate receptor function in schizophrenia."

The trials were carried out over 201 sites, with each trial including about 600 patients with persistent, predominant negative symptoms of schizophrenia. Patients treated with antipsychotics were administered placebo or bitopertin (5, 10, or 20 mg) for 24 weeks. The doses were chosen to test the minimal effective dose (5 mg) and the dose with a predicted maximal effect (20 mg).

All participants showed some improvement in the negative symptom factor score, but there were no differences between placebo or bitopertin treatment at 24 weeks. No differences were observed in other
symptom domains of schizophrenia either. All three doses of bitopertin were well-tolerated and generally safe over the course of the study.

According to Bugarski-Kirola, tackling complex clinical, regulatory and commercial development processes, reliability and quality control was a daunting task when dealing with over 200 study sites across different cultures. "We demonstrated that quality can be accomplished across the sites, but consider a different approach to the design," she said, explaining that rather than treating negative symptom patients as one homogenous target, priority should be given to exploring the usefulness of novel mechanisms in separate negative symptom domains to better define the target population and maximize the chance of success before launching large phase III trials.


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