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Original Investigation | June 2014

Effect of Bitopertin, a Glycine Reuptake Inhibitor, on Negative Symptoms of Schizophrenia

A Randomized, Double-Blind, Proof-of-Concept Study

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ABSTRACT

ABSTRACT | METHODS | RESULTS | DISCUSSION | CONCLUSIONS | ARTICLE INFORMATION | REFERENCES

Importance In schizophrenia, the severity of negative symptoms is a key predictor of long-term disability. Deficient signaling through the *N*-methyl-D-aspartate receptor is hypothesized to underlie many signs and symptoms associated with schizophrenia in particular negative symptoms. Glycine acts as an *N*-methyl-D-aspartate receptor coagonist. Blockade of the glycine transporter type 1 to inhibit glycine reuptake and elevate synaptic glycine concentrations represents an effective strategy to enhance *N*-methyl-D-aspartate receptor transmission.

Objective To determine the efficacy and safety of bitopertin (RG1678), a glycine reuptake inhibitor, in patients with schizophrenia and predominant negative symptoms who were stable while taking an antipsychotic treatment.

Design, Setting, and Participants This randomized, double-blind, placebo-controlled, phase 2 proof-of-concept trial involved 323 patients with schizophrenia and predominant negative symptoms across 66 sites worldwide.

Interventions Bitopertin (10, 30, or 60 mg/d) or placebo added to standard antipsychotic therapy for a treatment duration of 8 weeks.

Main Outcomes and Measures Change from baseline in the Positive and Negative Syndrome Scale negative factor score.

Results In the per-protocol population, 8 weeks of treatment with bitopertin was associated with a significant reduction of negative symptoms in the 10-mg/d (mean [SE] reduction in negative symptoms score, -25% [2%]; *P* = .049) and 30-mg/d (mean [SE], -25% [2%]; *P* = .03) bitopertin groups, a significantly higher response rate and a trend toward improved functioning in the 10-mg/d group when

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compared with placebo (mean [SE], -19% [2%]). Results reached trend-level significance in the intent-to-treat population. Estimates of bitopertin binding to glycine transporter type 1 showed that low to medium levels of occupancy yielded optimal efficacy in patients, consistent with findings in preclinical assays.

Conclusions and Relevance Bitopertin-mediated glycine reuptake inhibition may represent a novel treatment option for schizophrenia, with the potential to address negative symptoms.

Trial Registration clinicaltrials.gov Identifier: [NCT00616798](#)

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