Targeting Gene Mutation Alleviates Psychosis Symptoms

By Batya Swift Yasgur, MA, LSW

Treatment that targets a specific gene mutation can alleviate symptoms of psychosis in patients with psychotic disorders, results from a new proof-of-concept study show.

In two double-blind, placebo-controlled trials, investigators studied a mother and a son, each of whom had a different psychotic disorder but carried the same rare genetic mutation—a copy number variant (CNV) involving four, instead of the usual two, copies of the gene that encodes glycine decarboxylase (GLDC).

In the first trial, the patients’ existing psychopharmacologic regimen was augmented with glycine. In the second trial, it was augmented with D-cycloserine (DCS). Both are coagonists of the N-methyl-D-aspartate (NMDA) receptor (Glycine is a full coagonist; DCS is a partial coagonist).

With both agents, symptoms of psychosis improved. Glycine was associated with significant gastrointestinal (GI) side effects, whereas DCS was well tolerated.

“We think we have found a pretty good bridge from genomic analysis to pathophysiology to treatment,” coauthor Uwe Rudolph, MD, former director of the Laboratory of Genetic Neuropharmacology, Basic Neuroscience Division, McLean Hospital, Boston, Massachusetts, and former professor of psychiatry, Harvard Medical School, Cambridge, Massachusetts, told Medscape Medical News.

“We consider this an early example of personalized medicine in psychiatry,” said Rudolph, who is currently professor of comparative biosciences at the University of Illinois at Urbana-Champaign.

The study was published online July 3 in Biological Psychiatry.

Structural Rearrangement

Individually, rare structural variants such as CNVs “collectively account for an increased mutational burden for schizophrenia and other neurodevelopmental disorders.” The most recurrent are microdeletions and microduplications, the authors write.

“The fact that shared molecular mechanisms are implicated in a range of neurodevelopmental disorders suggests that a genotype-first approach may be more instructive about pathophysiology and potential treatments than a disease-focused approach,” they add.

“We were doing a study looking for CNVs—large structural changes in the genome in patients with schizophrenia and their biological family members. In the course of running those assays, we came across a particular mutation in a patient and his mother,” senior author Deborah L. Levy, PhD, director, Psychology Research Laboratory, McLean Hospital, Boston, told Medscape Medical News.

The mother (“patient 5459”) and son (“patient 3363”) both had psychotic illnesses—schizoaffective disorder and bipolar disorder with psychotic features, respectively.
The researchers identified several CNVs spanning 9p24.1 in both the patient and his mother.

“One particular mutation involved a structural rearrangement that included a triplication of the glycine decarboxylase gene. Having four copies of this gene would be expected to increase activity of this enzyme and lower levels of glycine in the brain,” she continued.

Glycine plays an important role in NMDA receptor function, and NMDA receptor dysfunction has been implicated in the pathophysiology of schizophrenia, “so if the glycine modulatory site is not fully occupied, the receptor will not fire normally when glutamate arrives at its location on the receptor,” she explained.

Previous studies have investigated the use glycine to boost the NMDA receptor’s functionality, but in those studies, patients were selected for being treatment refractory and were not selected on the basis of having an identified problem involving glycine or the NMDA receptor, Levy noted.

**Glycine: Limited Clinical Utility**

The researchers began with a glycine double-blind, random-order, glycine-placebo crossover augmentation trial. This was followed by a trial of open-label glycine.

In each of the three study arms, treatment was administered for 6 weeks. Following each 6-week treatment period was a 2-week washout period to eliminate effects of the previous treatment.

Formal clinical ratings, determined on the basis of a variety of instruments (e.g., the Brief Psychiatric Rating Scale [BPRS]), were obtained every 2 weeks.

The two patients continued to take stable doses of their psychotropic medications. These medications were augmented by a starting dose of 6 g of glycine daily; glycine was titrated upward by 3 g/day until the target dose was reached or GI side effects occurred.

Each of the two patients showed improvement in clinical symptoms during administration of glycine.

For patient 5459, during the arms of the double-blind trial, the mean (SD) total BPRS score was 30.3 (8.6) while on glycine, vs 35.0 (3.5) while off glycine.

For patient 3363, the mean total BPRS score was 25.0 (6.2) while on glycine, vs 35.0 (6.1) while off glycine.

The estimated magnitude of effect (i.e., mean [SE] decrease in total BPRS score while receiving glycine) was 7.3 (3.0) points (20%) lower than while receiving placebo, but the difference did not reach statistical significance (P = .083).

The effect of glycine on total BPRS score did not differ significantly between patients.

During the subsequent 6 weeks of open-label treatment with glycine, both patients again showed a substantial reduction of symptoms, but following completion of that arm, both patients experienced an exacerbation of clinical symptoms during the 8-month interval between the end of the short-term trial and the beginning of the open-label long-term trial.

Although both patients showed an initial reduction in total BPRS score, the long-term glycine trial was temporarily suspended at 16 weeks, because GI side effects became intolerable.

Both patients asked that the trial end during week 47 because of chronic GI side effects, which occurred even when doses of glycine were reduced. The maximum sustainably tolerable doses were ~18.8% to 27.5% of the target doses.

The mean (SE) decrease in total BPRS score while receiving glycine in all open-label periods was 8.8 (1.5) (P < .001)—a
reduction of 26%.

“The sad fact is that glycine is impossible to use as an ongoing treatment because it has chronic GI side effects, so although it’s a nice laboratory method of testing response — increasing glycinergic NMDA receptor activity—the clinical significance is limited by the impracticality of sustained treatment with glycine,” lead author J. Alexander Bodkin, MD, director, Clinical Psychopharmacology Research Program, McLean Hospital, told Medscape Medical News.

**Remarkably Effective**

In the DCS trial, the researchers used a similar model.

The first arm was an 8-week open-label trial, after which the two patients underwent a 1-week washout period, which was deemed sufficient for the 7- to 15-hour half-life of DCS. The double-blind placebo-controlled trial then started.

Each arm lasted 6 weeks, with a 1-week washout period between arms. The double-blind phase was followed by 24 weeks of open-label exposure. DCS was administered at a dose of 50 mg every morning.

Both patients showed marked improvement in clinical symptoms during the period they were administered DCS.

During the two arms of the double-blind trial, the mean (SD) total BPRS score for patient 5459 was 28.3 (1.5) while on DCS, vs 34.3 (1.2) while off DCS.

For patient 3363, the mean (SD) total BPRS score was 25.3 (0.6) while on DCS, vs 42.7 (4.0) while off DCS. This patient showed improvement in both positive and negative symptoms of psychosis.

During the double-blind phase, the estimated magnitude of effect (i.e., mean [SE] decrease in total BPRS score while receiving DCS) was 11.7 (1.1) points, 30.3% lower than while receiving placebo (P = .006).

During the short-term and long-term open-label periods, the mean (SE) decrease in total BPRS score while receiving DCS was 3.8 (2.1) (P < .009), a mean reduction of 12.7%.

Levy explained that glycine does not readily cross the blood-brain barrier, so high doses must be divided and administered throughout the day. Eventually, at optimal therapeutic dose, GI side effects become intolerable.

“So, we thought we would try DCS, which is a partial agonist at the NMDA receptor. Although not as potent, it does cross the blood-brain barrier more readily, but without the complications of glycine and with easier dosing,” she added.

“We thought we might get a lesser clinical response with DCS because, as a partial agonist, it is less potent that glycine, but we got a much better clinical response,” Bodkin reported.

He noted that DCS can be “remarkably effective when clear glycinergic hypofunction is present.”

**Umbrella Designation**

Rudolph noted that schizophrenia is an “umbrella designation” for people who may have substantially different genetic makeups and clinical presentations.

“In psychiatric disorders, with schizophrenia as the most extreme example, the diagnoses we use are overinclusive—you can be sitting with six people who meet full diagnostic criteria for a given disorder but have little in common,” Bodkin elaborated.

Conversely, Rudolph pointed out, “our patients had the same mutation but not the same diagnosis — and yet both showed
marked symptom improvement.”

For that reason, to “move beyond this very limited level of therapeutic power that psychopharmacology is currently yielding, we have to be able to more accurately classify the underlying biology in different patients,” Bodkin noted.

“In our study, we had an identified lesion likely to be of pathophysiological importance that had a significant clinical effect when pharmacologically corrected,” Rudolph stated.

Levy added that many clinical trials of compounds that act at the NMDA receptor, such as glycine and DCS, exclude patients who are undergoing treatment with clozapine because of concern that clozapine would have such a beneficial effect that further improvement would not be seen.

But “it is clear from our study that treatment with clozapine did not prevent further improvement from being detected,” she noted.

**Precision Medicine**

Commenting on the study in a press release, John Krystal, MD, editor of Biological Psychiatry, said, “Psychiatry is in the very early days of precision medicine—i.e., the effort to match particular patients to the specific treatment they need.”

The researchers “provide a wonderful example of this approach,” he added.

Bodkin agreed, adding that current treatments for schizophrenia are “nonspecific—very helpful to some people but not to others.”

These “global interventions” not only are sometimes ineffective but are also costly and may have side effects.

“Our study may be the beginning of a project that will allow us to address an underlying problem without unnecessary side effects,” he said.

The investigators told Medscape Medical News that because of the rarity of these genetic mutations, “small N studies will be the norm.

“Proof-of-principle studies like this one can only be carried out if carriers of these rare mutations are willing to be involved as collaborators in research. It is thus important to recognize the vital role of patients in advancing science.”

The investigators expressed their gratitude to the trial participants for their willingness to undergo “a pretty arduous set of procedures over an extended period of time. We could not have conducted this research without their cooperation.”

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