

Placebo-Controlled Trial of Glycine Added to Clozapine in Schizophrenia

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Objective: The purpose of this study was to evaluate the effects of high-dose oral glycine on positive and negative symptoms and cognitive function when added to clozapine in adults with schizophrenia.

Method: The authors conducted a double-blind, placebo-controlled, parallel-group trial of 60 g/day of glycine added to

clozapine for 8 weeks in 30 adults with schizophrenia. Clinical ratings were performed every 2 weeks.

Results: Twenty-seven patients completed the trial. Glycine augmentation of clozapine produced no statistically significant change in positive or negative symptoms or cognitive functioning. No subjects showed clinically significant worsening of clinical ratings.

Conclusions: These data, combined with data from previous trials with D-cycloserine and glycine, suggest that agonists at the glycine site may be less effective when combined with clozapine than they are when combined with conventional antipsychotics.

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Several lines of evidence have converged to implicate a role for glutamatergic activity in clozapine's superior effectiveness in the treatment of schizophrenia. In previous studies, we found that patients treated with clozapine had significantly higher serum glutamate levels than patients treated with conventional agents (1); that serum glutamate and aspartate levels increase when patients are switched from conventional neuroleptics to clozapine (2); and that lower glycine levels in patients receiving conventional agents were associated with more robust improvement in negative symptoms after conversion to clozapine (2). D-Cycloserine, a partial agonist at the glycine site of the N-methyl-D-aspartic acid (NMDA) receptor, lowered negative symptoms by 22% when added to conventional neuroleptics (3) but raised negative symptoms by 21% when added to clozapine (4).

As a partial agonist at the glycine site, D-cycloserine may act as an agonist or antagonist depending on the concentration of endogenous ligand, the dose of D-cycloserine, or the functional state of the NMDA receptor (5). Systemic administration of glycine has been shown to block behavioral effects of NMDA antagonists (6, 7), suggesting that the glycine binding site associated with the NMDA receptor is not fully saturated in the mammalian brain.

Reports of glycine augmentation in patients with schizophrenia have also pointed to a difference between clozapine and conventional antipsychotics. The addition of 60 g/day of glycine (8, 9) and 30 mg/kg per day of serine (10) to the conventional antipsychotic treatment of patients significantly improved negative symptoms, but 30 g/day of glycine added to clozapine was associated with no change in negative symptoms (11). If the glycine receptor is fully or nearly fully activated during clozapine treat-

ment, the partial agonist D-cycloserine may worsen negative symptoms by competitive antagonist effects. In contrast, glycine, a full agonist, would not be expected to worsen or improve negative symptoms when added to clozapine.

Method

The study was approved by the appropriate institutional review boards. After complete description of the study to the subjects, written informed consent was obtained. Thirty clinically stable outpatients with schizophrenia diagnosed by DSM-IV criteria were enrolled. Inclusion criteria included a score of 27 or greater on the Scale for the Assessment of Negative Symptoms (SANS), treatment with a stable dose of clozapine for at least 4 weeks, and no other antipsychotic medications in oral form for at least 3 months or in depot form for 6 months. Patients with current major depressive episode or substance abuse were excluded.

The patients underwent a 2-week single-blind placebo lead-in followed by an 8-week randomly assigned double-blind treatment phase with 30 g of glycine in 7 ounces of lemonade twice a day or a similar-tasting and identical-appearing placebo mixture. Stable solutions of glycine were made biweekly from bulk powder. Clozapine was continued unchanged.

Measures used for biweekly assessments included the Brief Psychiatric Rating Scale (BPRS), SANS, Positive and Negative Syndrome Scale, Global Assessment Scale, and Simpson-Angus Rating Scale. The Hamilton Depression Rating Scale was administered at baseline. Tests for cognitive functioning performed at baseline and week 8 included the Stroop; WAIS vocabulary, information, digit span, and block design subtests; California Verbal Learning Test; finger tapping; and judgment of line orientation. Serum for amino acid measurement was sampled between 10:00 a.m. and 2:00 p.m. at baseline and week 8.

Results

Two patients dropped out during the single-blind placebo phase, and one patient dropped out on day 4 of gly-

TABLE 1. Clinical Ratings for 27 Patients With Negative Symptoms of Schizophrenia at Baseline and After 8 Weeks of Treatment With Glycine (60 g/day) or Placebo

Measure	Glycine (N=14)					Placebo (N=13)					Analysis ^a		
	Baseline		Week 8		%	Baseline		Week 8		%			
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		t	df	p
SANS													
Total	52	16	50	17	-4	58	14	59	14	0	0.77	25	0.45
Affect	17	5	16	4	-6	17	5	18	6	6	0.97	25	0.34
Alogia	7	3	6	4	-14	9	4	9	5	0	0.59	25	0.56
Apathy	9	4	10	3	3	11	2	10	2	-7	-1.20	25	0.21
Anhedonia	13	4	12	6	-9	15	3	16	2	7	1.60	25	0.11
Attention	6	5	6	4	0	6	4	6	4	0	0.33	25	0.74
Positive and Negative Syndrome Scale													
Total	70	10	67	15	-4	75	11	71	10	-5	0.14	25	0.88
Positive	15	4	14	4	-7	17	4	14	3	-18	-1.50	25	0.14
Negative	20	5	20	6	0	22	5	22	5	0	0.45	25	0.65
Brief Psychiatric Rating Scale (BPRS) ^b	39	7	37	7	-5	44	7	39	8	-11	-4.60	23	0.37
Global Assessment Scale (GAS) ^b	49	9	54	7	10	49	6	49	6	0	-1.70	22	0.09

^a Student's t test was used to compare difference between patients given glycine or placebo in percent change from baseline.

^b Five subjects could not be included in the analysis: two subjects did not have complete baseline BPRS data, and three subjects did not have baseline GAS data.

cine treatment. One patient receiving glycine stopped all medications during week 5 and required hospitalization; this subject's final assessment at week 4 was carried forward for statistical analysis. Although an adverse effect of glycine cannot be ruled out in this patient, ratings of psychosis and general psychopathology were lower at week 4 than baseline. No patient met the placebo response criterion (20% improvement in total SANS) during the placebo lead-in phase. Clinical staff observed medication administration in 10 of the 14 subjects randomly assigned to receive glycine.

We analyzed results from 27 patients. Six were women, and 21 were men; their mean age was 39 years (SD=7), mean duration of illness was 16 years (SD=7), mean clozapine dose was 455 mg/day (SD=116), mean baseline Hamilton depression scale score was 13 (SD=7), and mean Simpson-Angus Rating Scale score was 3 (SD=2). Fourteen patients received glycine, and 13 received placebo. There was no significant difference between the glycine and placebo groups in age, clozapine dose, or duration of illness. Change scores on all clinical measures, analyzed by using Student's t test, showed no significant treatment effect (Table 1). Ninety-five percent confidence intervals for the change from baseline to week 8 for the glycine group and for the difference between the glycine and placebo groups included zero for all clinical and cognitive scales. Repeated measures analysis of variance revealed no significant treatment effect on any measure of positive or negative symptoms from baseline through week 8: SANS total ($F=1.5$, $df=4$, 24 , $p=0.21$); Positive and Negative Syndrome Scale total ($F=1.1$, $df=4$, 24 , $p=0.35$), positive subscale ($F=0.7$, $df=4$, 24 , $p=0.58$), and negative subscale ($F=0.4$, $df=4$, 24 , $p=0.81$); and BPRS ($F=1.1$, $df=4$, 22 , $p=0.38$).

Mean serum glycine at baseline was 239 $\mu\text{mol/liter}$ (SD=41); mean serum glycine at week 8 was 1390 $\mu\text{mol/liter}$ (SD=1033). One patient had less than a three-fold increase in serum glycine. With that patient excluded, the mean in-

crease in glycine levels was sixfold. Mean serum serine at baseline was 87 $\mu\text{mol/liter}$ (SD=17); mean serine at week 8 was 274 $\mu\text{mol/liter}$ (SD=195).

Discussion

Consistent with the recent report by Potkin et al. (11), high-dose glycine did not improve negative symptoms when added to clozapine. However, we did not observe the relative worsening of positive symptoms detected by Potkin et al. Our finding of 4% improvement in SANS scores is in marked contrast to previous reports of 17%–30% improvement when a comparable dose of glycine was added in patients primarily treated with conventional agents (8, 9). Both D-cycloserine and glycine appear to produce different responses when added to conventional neuroleptics than they do when added to clozapine (1, 3, 4, 10).

This is a small study of relatively short duration with a possibility of type II error. A longer trial with more subjects may be required to observe change in negative symptoms. However, previous studies with glycine using smaller samples and lasting 6 and 8 weeks have demonstrated significant improvement in negative symptoms (8, 9). Also, this study was performed in an outpatient setting, where compliance could not be ensured and observations were limited to biweekly evaluations. However, most of the patients were living in residences with supervised medication administration, and glycine levels indicated they were compliant with the study drug.

These data, combined with data from previous trials with D-cycloserine and glycine, suggest that agonists at the glycine site may be less effective when combined with clozapine than with conventional antipsychotics. These data also add to a growing body of evidence suggesting that relative activity at the glycine site of the NMDA receptor may contribute to differences in clinical efficacy between conventional and novel antipsychotic medications.

BRIEF REPORTS

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