

# Efficacy of High-Dose Glycine in the Treatment of Enduring Negative Symptoms of Schizophrenia

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**Background:** Disturbances of *N*-methyl-D-aspartate (NMDA) receptor-mediated glutamatergic neurotransmission may play an important role in the pathophysiology of negative symptoms of schizophrenia. Glycine, a small non-essential amino acid, functions as an obligatory coagonist at NMDA receptors through its action at a strychnine-insensitive binding site on the NMDA receptor complex. Glycine-induced augmentation of NMDA receptor-mediated neurotransmission may thus offer a potentially safe and feasible approach for ameliorating persistent negative symptoms of schizophrenia.

**Methods:** Twenty-two treatment-resistant schizophrenic patients participated in a double-blind, placebo-controlled, 6-week, crossover treatment trial with 0.8 g/kg per day of glycine added to their ongoing antipsychotic medication. Clinical assessments, including the Brief Psychiatric Rating Scale (BPRS), the Positive and Negative Syndrome Scale (PANSS), the Simpson-Angus Scale for Extrapyramidal Symptoms, and the Abnormal Involuntary Movement Scale, were performed biweekly through-

out the study. Clinical laboratory values and amino acid serum levels were monitored.

**Results:** Glycine treatment was well tolerated and induced increased glycine ( $P = .001$ ) and serine ( $P = .001$ ) serum levels. Glycine administration resulted in (1) a significant ( $P < .001$ )  $30\% \pm 16\%$  reduction in negative symptoms, as measured by the PANSS; and (2) a significant ( $P < .001$ )  $30\% \pm 18\%$  improvement in the BPRS total scores. The improvement in negative symptoms was unrelated to alterations in extrapyramidal effects or symptoms of depression. Low pretreatment glycine serum levels significantly predicted ( $r = 0.80$ ) clinical response.

**Conclusion:** These findings support hypoglutamatergic hypotheses of schizophrenia and suggest a novel approach for the pharmacotherapy of negative symptoms associated with this illness.

*Arch Gen Psychiatry.* 1999;56:29-36

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**D**EFICITS IN glutamatergic functioning,<sup>1-9</sup> particularly involving neurotransmission at *N*-methyl-D-aspartate (NMDA)-type glutamate receptors,<sup>10-13</sup> are postulated to play a key role in the pathophysiology of schizophrenia. The NMDA receptors are stimulated not only by glutamate but also by glycine, an amino acid that acts as an obligatory coagonist at the strychnine-insensitive glycine modulatory site of the NMDA receptor.<sup>14,15</sup> The ability of glycine to potentiate NMDA receptor-mediated neurotransmission, along with the fact that it is well tolerated during both acute and long-term administration, has raised the possibility that it may serve as an effective treatment for neuroleptic-resistant negative symptoms in schizophrenia. The normal diet contains approximately 2 g of glycine per day. Dietary glycine does not normally influence brain glycine levels.<sup>16</sup> When administered in sufficient quantity, however, peripherally administered glycine may pass the blood-brain barrier and functionally elevate brain glycine levels.<sup>17-21</sup>

To date, 7 studies have investigated the effects of glycine in schizophrenia.<sup>22-28</sup> The first controlled glycine trial,<sup>27</sup> which used a glycine dose of 15 g/d, demonstrated significant global improvement during glycine treatment and a trend toward improvement on the Brief Psychiatric Rating Scale (BPRS).<sup>29</sup> A subsequent controlled study,<sup>28</sup> using a glycine dose of approximately 30 g/d, found a significant 17% reduction in negative symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS).<sup>30</sup>

*See also pages 13 and 21*

In the present study, a glycine regimen of 0.8 g/kg per day, corresponding to a mean dose of approximately 60 g/d, was used within the framework of a double-blind, placebo-controlled, crossover

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## SUBJECTS AND METHODS

### SUBJECTS

This study was performed at Ezrath Nashim-Herzog Memorial Hospital, Jerusalem, Israel. Subjects were all inpatients who fulfilled the following inclusion criteria: (1) *DSM-IV*<sup>32</sup> diagnosis of schizophrenia, established on the basis of semistructured psychiatric interviews, review of all available medical records, and confirmation by at least 2 board-certified psychiatrists; and (2) treatment resistance established on the basis of at least 3 periods of treatment during the course of illness without satisfactory response, using antipsychotic drugs from at least 2 different classes, in doses equivalent to at least 1000 mg/d of chlorpromazine for at least 6 weeks; no period of good functioning within the preceding 5 years; and prestudy PANSS positive and negative symptom scores in the 70th percentile or higher, based on normative data for inpatients with chronic schizophrenia.<sup>30</sup> To be eligible, patients had to have been treated with a stable, clinically determined, optimal oral dose of a conventional or atypical antipsychotic for at least 3 months. Schizophrenic patients who met the criteria of additional *DSM-IV* diagnoses, were receiving additional psychotropic medications, or had a concurrent medical or neurologic illness were excluded. Complete medical and neurologic examinations, including laboratory tests, were performed before trial inclusion.

The research protocol was approved by the institutional review board at Ezrath Nashim-Herzog Memorial Hospital. Written informed consent was obtained from inpatients fulfilling the inclusion criteria and, whenever available, from their first-degree relatives, after the study had been described to them orally and in writing. A total of 22 patients were enrolled in the study (**Table 1**). All subjects receiving conventional neuroleptics had undergone, during the course of their illness, treatment trials with atypical antipsychotics (ie, clozapine and/or risperidone) that had been interrupted due to adverse effects and/or cost-effectiveness considerations.

### STUDY DRUG ASSIGNMENT AND TREATMENT

After a 2-week (weeks -2 to 0) baseline assessment period, subjects were randomly assigned to receive, under double-blind conditions, either glycine powder dissolved in water (20% solution) or an appearance- and taste-matched placebo (glucose) solution for 6 weeks. Glycine or placebo were given in addition to each patient's regular antipsychotic medication, the dose of which remained fixed throughout the study. Following completion of the first treatment phase (weeks 0-6), patients underwent a 2-week adjuvant (ie, glycine or placebo) treatment washout period (weeks 6-8), during which they continued to receive their regular antipsychotic medications. After the washout period, they crossed over to the alternate adjuvant treatment for a final 6 weeks (weeks 8-14).

Glycine administration was initiated at a dose of 4 g/d and was increased by 4 g/d until a fixed daily dose equivalent to 0.8 g/kg of body weight was reached after 9 to 19 treatment days (mean  $\pm$  SD, 14.0  $\pm$  2.7 days). The range of fixed daily glycine doses was 40 to 90 g (mean  $\pm$

SD, 61.2  $\pm$  13.4 g). Daily glycine treatment was administered in 3 divided doses.

Patients needing antiparkinsonian medication received individually determined, fixed doses of trihexypenidyl (dose range, 2-5 mg/d) throughout the study. Chloral hydrate (250-750 mg/d) was permitted as needed for treatment of insomnia or agitation.

### CLINICAL RATINGS

Symptoms and extrapyramidal effects were rated starting from week -2, biweekly, throughout the study, using the BPRS, the PANSS, the Simpson-Angus Scale for Extrapyramidal Symptoms<sup>34</sup> and the Abnormal Involuntary Movement Scale.<sup>35</sup> One trained research psychiatrist (C.M.) performed all ratings of the first 11 patients and a second one (M.E.) performed all ratings of the next 11 patients. The raters, the patients, and their families were unaware of and could not determine the study drug assignment by taste or otherwise. Patients requiring antipsychotic medication changes during the study were withdrawn from experimental treatment. Withdrawal decisions were based on clinical evaluations and coincided with a PANSS total score increase of at least 30%.

### BIOCHEMICAL MEASURES

Blood samples for assessment of glycine and serine serum levels were obtained at baseline and at the end of study weeks 6 and 14. Blood (5 mL) was drawn before breakfast and first daily medication administration, was immediately centrifuged for 5 minutes at room temperature and 1500g, and the supernatant was frozen at -80°C until analyzed. Plasma samples were deproteinized with sulfosalicylic acid. Amino acids were determined with an amino acid analyzer (Perkin Elmer Corp, Munich, Germany) using a lithium pH gradient and postcolumn derivation with ninhydrin. Quantification was carried out using a UV detector at 570 nm. Calculations were based on a *nor*-leucine internal standard. The intra-assay and interassay coefficients of variation were 1.5% and 2%, respectively; the lower limit of detection was 3.5 nmol/mL. In addition, blood was sampled biweekly throughout the study for assessment of hematologic, blood chemistry, liver function, and kidney function values.

### STATISTICAL ANALYSIS

Except for the midpoint analysis,<sup>31</sup> the blind was not broken before the last subject completed the study. Primary outcome analysis consisted of separate repeated-measures multivariate analyses of variance (MANOVAs) for positive, negative, cognitive, depressive, and excited factors of the PANSS.<sup>36</sup> Effect sizes (*f*) and confidence intervals (CIs) were derived from multivariate analyses along with statistical probability levels (*P*).

Secondary analyses evaluated change during treatment with glycine or placebo, considered independently, and relationships between change scores and potential response predictors, using Student *t* tests and Pearson product moment correlations (*r*). All statistic analyses were performed using SPSS for Windows (SPSS Inc, Chicago, Ill). All cited *P* values are 2 tailed, with a significance level of .05. Values are reported as mean  $\pm$  SD, followed by 95% CIs.

**Table 1. Demographic and Clinical Characteristics of the Sample\***

Age, y	38.8 ± 11.0
M/F	12/10
Sephardic/Ashkenazi	10/12
Years of schooling	8.4 ± 2.9
Age at first symptoms, y	18.9 ± 8.2
Age at first hospitalization, y	20.5 ± 7.6
No. of years since employment interruption	12.9 ± 10.5
Duration of present hospitalization, y	6.4 ± 5.9
No. of prior hospitalizations	8.4 ± 8.8
Cumulative lifetime duration of hospitalization, y	11.4 ± 9.3
Prestudy PANSS scores†	
Positive symptoms	26.5 ± 5.8
Negative symptoms	38.4 ± 6.2
Total	120.8 ± 25.4
Daily antipsychotic drug dose, mg/d‡	
Chlorpromazine equivalents (n = 15)	240.0 ± 146.3
Clozapine dose (n = 7)	471.0 ± 207.8

\*Values are mean ± SD for continuous variables and number of subjects for categorical values.

†PANSS indicates Positive and Negative Syndrome Scale. A 3-factor model<sup>30</sup> was used for assessment of prestudy levels.

‡Mean daily antipsychotic drug dose is given in chlorpromazine equivalents for 15 subjects who were receiving conventional antipsychotics, and in daily dose for 7 subjects receiving clozapine. The chlorpromazine equivalents were calculated using the equivalency criteria recommended by the New York State Office of Mental Health.<sup>33</sup>

design. A midpoint outcome assessment performed after the first 11 subjects completed the study suggested, as hypothesized, a significant reduction in negative symptoms following high-dose glycine.<sup>31</sup> The present report reflects final treatment outcome for the entire study group, with focus on identification of symptomatic and neurochemical predictors of glycine response.

## RESULTS

Of the 22 patients enrolled in the study, 19 completed both treatment phases. Ten patients were randomized to receive placebo during the first treatment phase; 9 received glycine. For all subjects, symptoms were stable for at least 2 weeks prior to study initiation (**Table 2**).

### PANSS FACTOR SCORES

Repeated-measures MANOVAs were performed with within-subject factors of treatment phase (placebo/glycine) and week within treatment phase (0, 2, 4, and 6 weeks). Highly significant, large effect size treatment effects were observed for negative and cognitive symptoms as well as for depression (**Table 3**). Glycine treatment led to a highly significant 30% ± 16% (95% CI, 26%-41%) decline in negative symptoms ( $t = 9.23$ ,  $df = 18$ ,  $P < .001$ ), whereas no significant change in negative symptoms was observed during placebo treatment (**Figure 1**). Cognitive symptoms ( $t = 6.15$ ,  $df = 18$ ,  $P < .001$ ) and depression ( $t = 3.6$ ,  $df = 18$ ,  $P < .01$ ) improved by 16% ± 11% (95% CI, 10%-21%) and 17% ± 21% (95% CI, 6%-27%), respectively, during treatment with glycine but not placebo. The treatment × time interaction remained significant, with large effect sizes for negative ( $F_{3,13} = 13.3$ ,

**Table 2. Five-Factor PANSS Scores Prestudy and at Initiation Study Week\***

PANSS Factor (wk 0)	Initial Assignment	Prestudy (Week -2)	Initiation
Positive symptoms	Glycine	14.8 ± 4.5	15.3 ± 4.1
	Placebo	16.6 ± 3.3	16.6 ± 3.1
Negative symptoms†	Glycine	30.6 ± 4.6	31.4 ± 3.9
	Placebo	35.0 ± 4.5	35.1 ± 4.6
Cognitive symptoms	Glycine	15.0 ± 4.7	15.8 ± 4.5
	Placebo	24.1 ± 5.8	24.1 ± 5.9
Excitement	Glycine	10.8 ± 4.2	10.7 ± 4.1
	Placebo	14.7 ± 4.6	14.0 ± 3.9
Depression	Glycine	12.6 ± 3.5	12.3 ± 3.6
	Placebo	14.4 ± 14.1	14.4 ± 4.0

\*Data are presented as mean ± SD. PANSS indicates Positive and Negative Syndrome Scale.

† $P < .05$ , patients assigned to receive glycine vs those assigned to receive placebo during first treatment phase.

$P < .001$ ,  $f = 0.75$ ) and cognitive symptoms ( $F_{3,13} = 3.8$ ,  $P < .05$ ,  $f = 0.5$ ), even following covariation for changes in depressive symptoms. Positive symptoms showed a significant 12% ± 20% (95% CI, 2%-20%) reduction during glycine treatment ( $t = 2.80$ ,  $df = 18$ ,  $P < .02$ ) and no significant change during placebo treatment. However, for positive symptoms, the treatment × time interaction was not significant (Table 3).

Along with reduction in PANSS scores, a significant 30% ± 18% (95% CI, 21%-40%) reduction in total BPRS scores was observed during treatment with glycine but not placebo ( $F_{3,16} = 8.9$ ,  $P = .001$ ,  $f = 0.6$ ). Fifteen (79%) of 19 subjects showed greater than 20% improvement in their symptoms during glycine treatment vs 2 (11%) of 19 subjects during placebo administration ( $\chi^2 = 15.3$ ,  $df = 1$ ,  $P < .001$ ). For PANSS negative symptom scores, 17 (90%) of 19 subjects showed greater than 20% improvement during glycine treatment vs 1 (5%) of 19 subjects during placebo administration ( $\chi^2 = 23.8$ ,  $df = 1$ ,  $P < .001$ ).

### ORDER EFFECTS

The effect of treatment order was assessed using MANOVA on PANSS change scores, with within-subject factor of week within treatment phase (2, 4, and 6) and between-subject factor of treatment order (glycine first vs placebo first). No significant treatment order effect was found for negative symptoms ( $F_{1,17} = 0.4$ ,  $P = .5$ ) or depression ( $F_{1,17} = 0.4$ ,  $P = .5$ ). However, an order effect was found for cognitive symptoms ( $F_{1,17} = 16.8$ ,  $P = .001$ ), such that the degree of improvement for subjects who received glycine second (21% ± 7%) was greater than for those who received it first (11% ± 13%) ( $F_{1,17} = 8.35$ ,  $P < .01$ ). The order effect was due, in part, to greater cognitive symptoms among patients randomized to receive glycine first, and became statistically nonsignificant when baseline cognitive symptoms were treated as a covariate ( $F_{1,16} = 0.7$ ,  $P > .4$ ). To evaluate effects of glycine free of any possible treatment order effect, analyses were performed in which

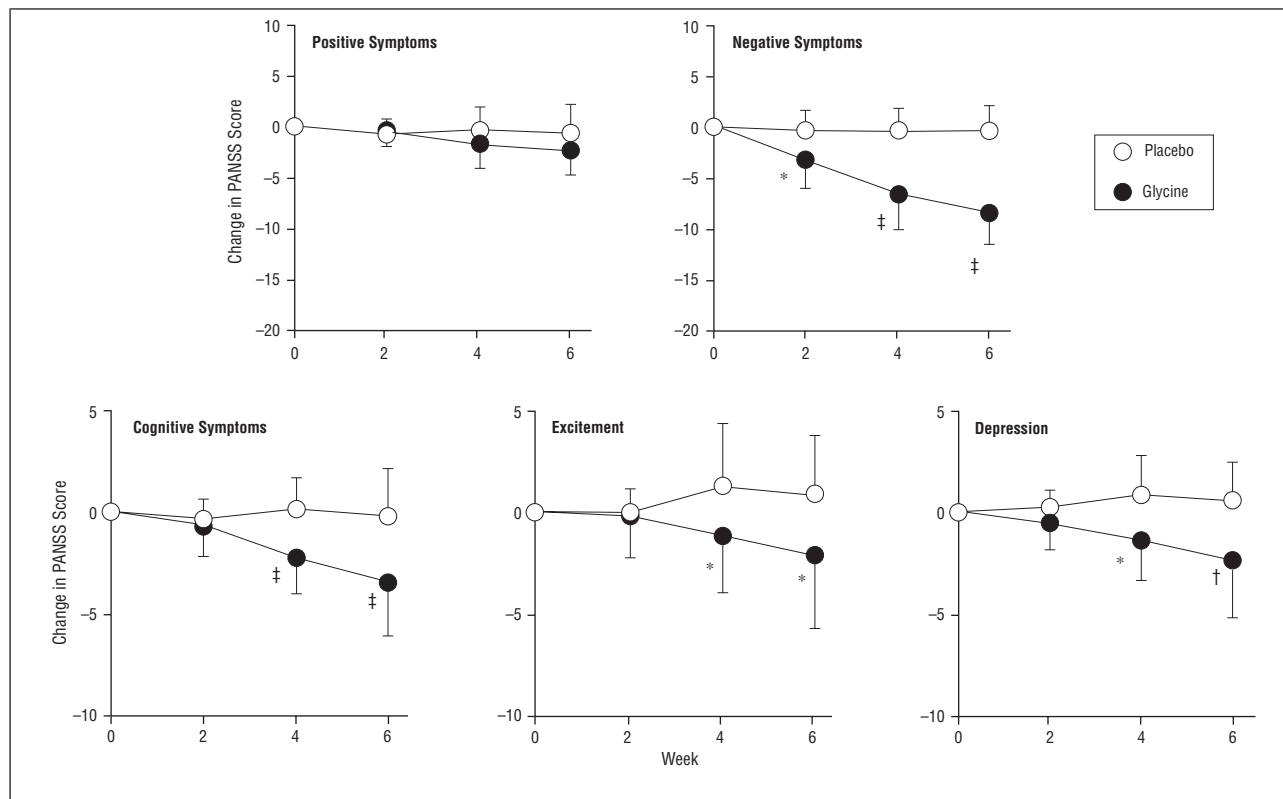
**Table 3. PANSS, SAS, and AIMS Scores by Treatment and Week\***

	Treatment Assignment	Week Within Treatment Phase				Treatment × Time (df = 3,16)†	Effect Size (f)‡
		0	2	4	6		
Positive symptoms	Glycine	16.0 ± 3.3	15.3 ± 3.4	14.3 ± 3.2	13.6 ± 2.9	F = 2.3, P>.2	...
	Placebo	15.2 ± 3.6	14.4 ± 4.1	14.8 ± 3.9	14.5 ± 3.7		
Negative symptoms†	Glycine	32.7 ± 5.0	29.4 ± 6.1	25.3 ± 7.1	22.2 ± 7.3	F = 21.8, P<.001	0.8
	Placebo	27.3 ± 10.5	26.9 ± 10.2	27.1 ± 10.0	27.0 ± 10.1		
Cognitive symptoms	Glycine	19.6 ± 6.9	18.9 ± 6.7	17.4 ± 5.7	16.1 ± 5.4	F = 7.6, P<.01	0.6
	Placebo	19.1 ± 7.2	18.8 ± 6.9	19.3 ± 6.8	19.0 ± 7.5		
Excitement	Glycine	13.0 ± 5.0	12.7 ± 4.2	11.8 ± 3.4	10.7 ± 3.4	F = 1.6, P>.2	...
	Placebo	10.9 ± 4.8	10.9 ± 4.4	12.2 ± 4.8	11.9 ± 4.8		
Depression	Glycine	13.9 ± 4.0	13.4 ± 4.1	12.5 ± 3.4	11.5 ± 4.1	F = 3.6, P<.05	0.4
	Placebo	12.1 ± 4.7	12.3 ± 4.6	13.0 ± 5.0	12.6 ± 5.2		
SAS	Glycine	1.3 ± 2.1	1.3 ± 2.1	0.9 ± 1.4	0.6 ± 0.8	F = 1.3, P>.3	...
	Placebo	1.2 ± 2.3	1.1 ± 2.2	1.0 ± 1.8	1.2 ± 2.0		
AIMS	Glycine	1.9 ± 3.7	1.8 ± 3.5	1.6 ± 3.3	1.4 ± 3.0	F = 1.6, P>.2	...
	Placebo	1.6 ± 3.3	1.7 ± 3.4	1.7 ± 3.5	1.9 ± 3.9		

\*Data are reported as mean ± SD unless otherwise indicated. PANSS indicates Positive and Negative Syndrome Scale; SAS, Simpson-Angus Scale for Extrapyramidal Symptoms; AIMS, Abnormal Involuntary Movement Scale; and ellipses, not applicable.

†For the Excitement subscale of PANSS, df = 3,15.

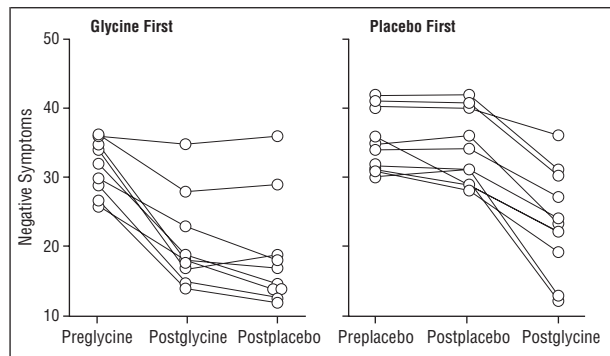
‡Effect size represents treatment × time interactions.



**Figure 1.** Effect of glycine and placebo treatment on factor scores (change scores) of the Positive and Negative Syndrome Scale (PANSS) derived using a 5-factor model<sup>36</sup> (n = 19). Asterisk indicates P<.05; dagger, P<.01; and double dagger, P<.001.

data were considered from only the first treatment phase. Even in this more limited data set, highly significant between-treatment differences were observed for negative symptoms ( $F_{3,15} = 9.2, P < .001, f = 0.6$ ).

Because 9 patients received glycine during the initial treatment phase, it was possible to observe the degree to which symptom improvement was maintained during the subsequent 8 weeks. Negative symptoms, which



**Figure 2.** Positive and Negative Syndrome Scale (PANSS) negative factor scores for individual patients treated initially with glycine (left) ( $n = 9$ ) or placebo (right) ( $n = 10$ ).

had declined significantly during the first treatment phase for patients receiving glycine (**Figure 2**, left), did not significantly increase during the subsequent placebo-treatment period, remaining significantly below pre-study levels 8 weeks following glycine discontinuation ( $t = 6.19$ ,  $df = 8$ ,  $P < .001$ ). For cognitive symptoms, there was some symptomatic reversal such that cognitive symptom scores 8 weeks following glycine discontinuation were no longer different from prestudy levels ( $t = 0.71$ ,  $df = 8$ ,  $P = .5$ ).

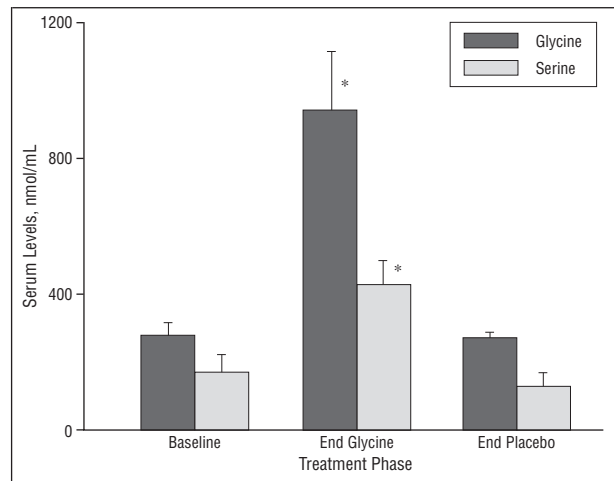
#### SERUM LEVELS OF AMINO ACIDS

Glycine treatment led to a highly significant 3.5-fold increase in serum glycine levels across subjects ( $t = 3.76$ ,  $df = 18$ ,  $P = .001$ ) (**Figure 3**). Symptom improvement was not significantly related to posttreatment serum glycine levels. In contrast, pretreatment serum glycine levels significantly predicted posttreatment PANSS negative, cognitive, and depression symptom scores, following 6 weeks of glycine treatment (**Figure 4**), as well as the degree of negative symptom improvement during glycine treatment ( $r = 0.80$ ,  $P < .001$ ).

Serine levels also increased significantly during glycine treatment (Figure 3). There were no significant correlations between serine levels and PANSS scores. A significant correlation was observed between glycine and serine levels across subjects at the end of glycine treatment ( $r = 0.72$ ,  $P = .008$ ), but not at other time points.

#### ADVERSE EFFECTS

Three patients (13%) did not complete the study. These patients did not differ significantly from other subjects in terms of demographic or clinical characteristics. Two patients were withdrawn, at study weeks 4 and 10 respectively, owing to psychotic exacerbations while receiving adjuvant placebo. The third patient was withdrawn at week 6 of glycine treatment because of upper gastrointestinal tract discomfort with nausea and vomiting that ceased following discontinuation of glycine treatment. Glycine and serine serum levels at withdrawal were 676 nmol/mL (reference range, 100-450 nmol/mL) and 491 nmol/mL (reference range, 75-200 nmol/mL), re-



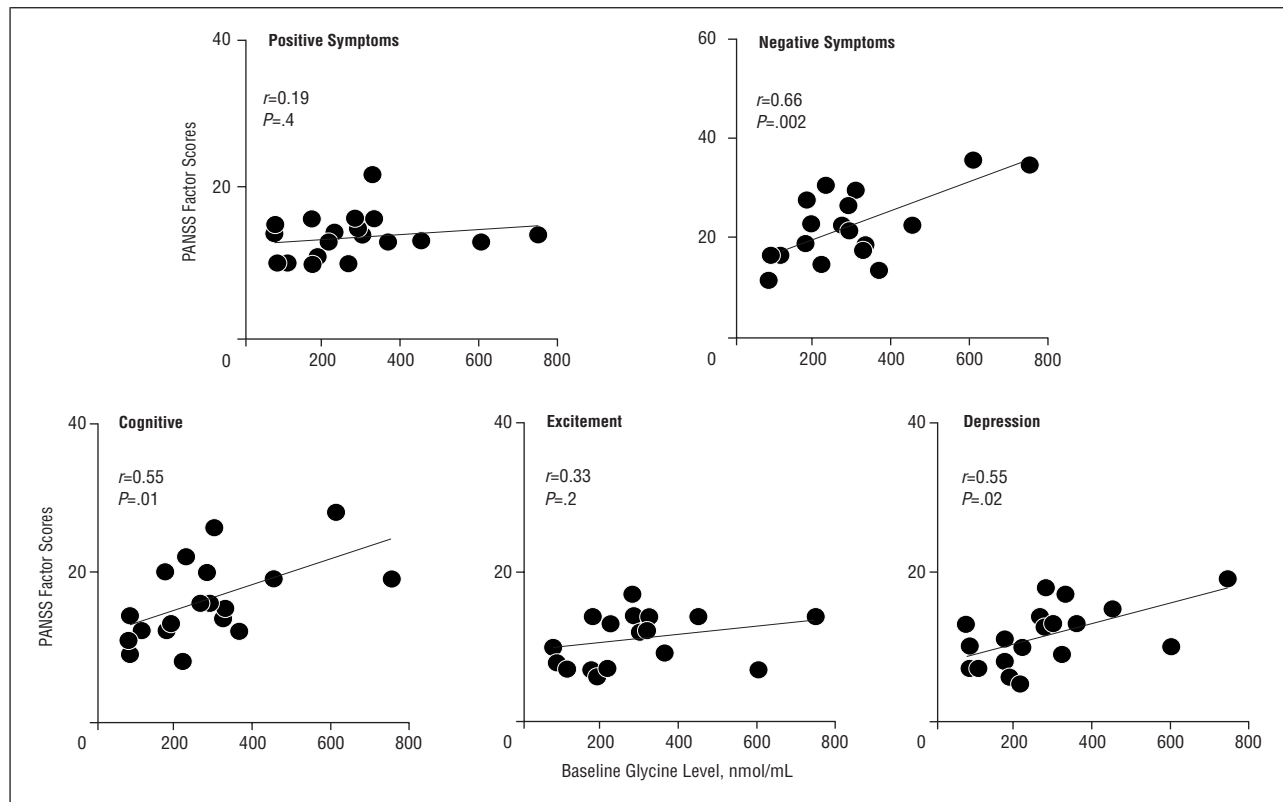
**Figure 3.** Mean  $\pm$  SD serum glycine ( $n = 19$ ) and serine ( $n = 12$ ) levels at baseline (glycine,  $278.3 \pm 174.4$  nmol/mL; serine,  $174.3 \pm 168.0$  nmol/mL) and during placebo (glycine,  $268.9 \pm 92.2$  nmol/mL; serine,  $131.2 \pm 38.8$  nmol/mL) and glycine (glycine,  $942.1 \pm 738.7$  nmol/mL; serine,  $430.3 \pm 228.6$  nmol/mL) treatment. Serine levels were not obtained for the initial 7 patients owing to technical reasons (unavailability of assay). Changes in level were significant with large effect size for glycine ( $F_{2,17} = 7.7$ ,  $P < .01$ ,  $f = 0.5$ ) and serine ( $F_{2,10} = 10.8$ ,  $P < .01$ ,  $f = 0.7$ ). Asterisk indicates  $P < .001$  vs baseline.

spectively. For all subjects, clinical laboratory parameters were unaffected by treatment.

Extrapyramidal effects and tardive dyskinesia scores were consistently low throughout the study and did not change significantly (Table 3). However, an approximate 50% reduction in scores on the Simpson-Angus Scale for Extrapyramidal Symptoms was observed during treatment with glycine but not placebo. To assess the potential influence of this effect on symptoms, change scores for each week within treatment phase were entered as covariates into MANOVAs. The treatment  $\times$  time interactions remained significant for negative ( $F_{2,15} = 23.8$ ,  $P < .001$ ,  $f = 0.8$ ) and cognitive ( $F_{2,15} = 3.9$ ,  $P < .05$ ,  $f = 0.3$ ) symptoms.

#### COMMENT

The primary finding of the present study is that treatment with 0.8 g/kg per day of glycine led to a significant 30%  $\pm$  16% across-subject reduction in negative symptoms in a sample of treatment-resistant inpatients with chronic schizophrenia. The improvement in negative symptoms was not accompanied by exacerbation of positive symptoms and could not be explained by changes in other symptom clusters or extrapyramidal symptoms, indicating that NMDA-based treatments may be effective in the treatment of what may be considered primary negative symptoms of schizophrenia.<sup>37</sup> The absence of a significant therapeutic effect of glycine on positive symptoms could reflect the fact that all patients were receiving antipsychotic medications and that the maximal therapeutic effect on positive symptoms had already been achieved prior to glycine administration. Alternatively, because NMDA antagonists induce negativelike symptoms to a greater degree than they induce positivelike symptoms, it is possible that NMDA receptor-based treatments for schizophrenia



**Figure 4.** Correlation between pretreatment serum glycine levels and Positive and Negative Syndrome Scale (PANSS) factor scores following 6 weeks of glycine treatment ( $n = 19$ ).

will prove to be minimally effective in the amelioration of specific positive symptoms.

During glycine treatment, a significant 3.5-fold increase in glycine serum levels was observed. Levels of serine, with which glycine interconverts,<sup>16</sup> were also increased, albeit to a lesser extent. The present study is the first in which glycine levels were measured prior to morning glycine administration (ie, trough levels). The finding that serum levels remained significantly elevated over baseline for as long as 12 hours after last administration indicates that the pharmacokinetics of glycine may be fundamentally altered following prolonged administration. In contrast, in challenge paradigms intravenous glycine has been found to return to baseline within 90 minutes of administration.<sup>19</sup>

Although all subjects enrolled in the study had initial serum glycine levels that were within or above the normal reference range, the degree of negative symptom improvement correlated significantly with pretreatment glycine serum levels; patients with the lowest baseline levels showed the greatest treatment-related improvement. This finding suggests that a relatively low pretreatment serum glycine concentration may serve as an effective predictor of responsiveness. Although cerebrospinal fluid<sup>4</sup> and brain tissue<sup>7</sup> glycine levels have been found to be relatively normal in schizophrenia, supranormal glycine levels may be required in this illness to induce optimal functioning of NMDA receptors. A correlation between serum glycine levels and clinical response was noted as well in a study<sup>38</sup> investigating effects of the partial glycine site agonist D-cycloserine.

Among subjects randomized to receive glycine first, reductions in negative symptoms that occurred during the first (ie, glycine) treatment phase were observed to persist for at least an additional 8 weeks (ie, throughout the washout period and subsequent placebo phase). This finding indicates either prolonged glycine effectiveness or permanent negative symptom change unrelated to glycine treatment. Twelve of the patients participating in this study participated in subsequent, unrelated drug studies. In that subset of patients, therefore, it was possible to assess the long-term persistence of negative symptom change following glycine withdrawal. The mean time from completion of glycine treatment to enrollment into a second trial for these patients was  $15.6 \pm 5.9$  months (range, 6-23 months). Negative symptom scores on the PANSS, which had declined from a pretreatment score of  $38.4 \pm 7.3$  to a score of  $27.1 \pm 0.8$  in these patients, returned during the poststudy interval to a score of  $36.8 \pm 6.5$ . Thus, while the glycine-induced reduction in negative symptoms that occurred during this study was found to persist during a period of several weeks, it resolved during a period of several months.

The persistence of negative symptom improvement, which warrants further investigation, could reflect several factors. First, delayed relapse is often seen with conventional antipsychotics, and is thought to reflect drug accumulation in tissue with subsequent slow release.<sup>39-41</sup> With depot preparations, the relapse may be even more protracted, often occurring after the apparent disappearance of the drug from plasma.<sup>42,43</sup>

Even following such disappearance, sufficient drug amounts for inducing receptor occupancy may exist in the brain.<sup>43</sup> Similarly, prolonged high-dose glycine treatment may saturate glycine reservoirs in the brain, resulting in prolonged activation of NMDA receptor glycine modulatory sites and persistence of some therapeutic effects despite interruption of glycine administration.

The persistence of glycine effects could also reflect enhancement of the efficacy of ongoing antipsychotic drug treatment. The nature of this hypothesized interaction would remain to be determined, since it is unlikely that it could be related to glycine-induced alterations of neuroleptic levels. Glycine has been found not to alter central nervous system neuroleptic levels in mice<sup>28</sup> and not to alter serum levels in patients.<sup>21</sup> Furthermore, subjects included in this study had been previously exposed to a wide variety of antipsychotic drugs and doses, without substantially better functioning than at the time of enrollment into this study. Nevertheless, because serum neuroleptic levels were not obtained during the study, the possibility of a pharmacokinetic interaction between glycine and antipsychotic drugs remains open. Finally, NMDA receptor activation is associated with induction of neuronal plasticity. Processes initiated by increased NMDA transmission, such as long-term potentiation<sup>44</sup> or alterations in gene expression patterns,<sup>45,46</sup> may resolve over weeks even after the level of NMDA transmission has returned to baseline.

Limitations of the present study include relatively small sample size and assessment of glycine cognitive effects based on clinical ratings rather than neuropsychological examination. In addition, glycine safety and efficacy during long-term, maintenance administration needs to be evaluated.<sup>47,48</sup> Assessment of these aspects of glycine treatment in controlled, larger-scale studies seems warranted. By indicating that high-dose glycine treatment may be both efficacious against persistent negative symptoms and devoid of substantial adverse effects, the present study brings pivotal support to the concept of modulation of NMDA receptor-mediated neurotransmission as an innovative pharmacological strategy in schizophrenia.

Accepted for publication July 23, 1998.

This research was supported by grants from the Hebrew University–Milton Rosenbaum Endowment Fund for Research in Psychiatric Sciences, and the Harry Stern/ENOSH Research Fund (Dr Heresco-Levy), Jerusalem, Israel; the National Alliance for Research on Schizophrenia and Depression, Chicago, Ill; and grant MH56343 from the National Institute of Mental Health, Rockville, Md (Dr Javitt).

This study had no commercial sponsorship.

Parts of this article were presented at the symposium "Phencyclidine Model of Schizophrenia: From Theory to Practice," at the annual meeting of the American Psychiatric Association, San Diego, Calif, May 20, 1997.

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