ORIGINAL ARTICLE

Sarcosine or D-Serine Add-on Treatment for Acute Exacerbation of Schizophrenia

A Randomized, Double-blind, Placebo-Controlled Study

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Context: Agents that enhance *N*-methyl-D-aspartate (NMDA) function through the glycine modulatory site (D-serine, glycine, or D-cycloserine) or through glycine transporter 1 (sarcosine) improve the symptoms of patients with stable chronic schizophrenia.

Objective: To determine whether NMDA-glycine site agonists or glycine transporter-1 inhibitors have better efficacy and whether NMDA receptor–enhancing agents have beneficial effects for acute exacerbation of schizophrenia.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Inpatient units of 2 major medical centers in Taiwan.

Patients: Sixty-five schizophrenic inpatients with acute exacerbation.

Interventions: Six weeks of treatment with sarcosine (2 g/d), D-serine (2 g/d), or placebo and concomitant optimal risperidone therapy.

Main Outcome Measures: Positive and Negative Syndrome Scale (PANSS) and Scale for the Assessment of Negative Symptoms (SANS) (20 and 17 items) total scores.

Results: The sarcosine group revealed more reductions in PANSS total scores than the placebo ($P=.04$) and D-serine ($P<.001$) groups. Sarcosine adjunctive treatment was also superior to placebo in reducing SANS-20 ($P=.007$) and SANS-17 ($P=.003$) scores and to D-serine in decreasing SANS-20 ($P=.006$) and SANS-17 ($P=.002$) scores. The PANSS-general, PANSS-cognitive, and PANSS-depressive symptoms scores and SANS-alogia and SANS–blunted affect scores improved significantly more in sarcosine-cotreated patients than in risperidone monotherapy patients ($P\leq.02$ for all). Sarcosine adjunctive therapy also surpassed D-serine in terms of PANSS-general, PANSS-positive, PANSS-negative, and PANSS-depressive symptoms scores ($P\leq.04$ for all). D-Serine and risperidone cotreatment did not differ significantly from risperidone monotherapy in all efficacy domains.

Conclusions: This first short-term treatment study on NMDA receptor–enhancing agents suggests that sarcosine, superior to D-serine, can benefit not only patients with long-term stable disease but also acutely ill persons with schizophrenia. This finding indicates that a glycine transporter 1 inhibitor may be more efficacious than NMDA-glycine site agonists for adjuvant treatment of schizophrenia, at least during the acute phase. Further studies are needed.

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TREATMENT RESPONSE TO acute exacerbation of schizophrenia is often incomplete, and patients are frequently left with significant residual symptoms and functional impairments.[1] Because schizophrenic psychosis can be a detrimental biopsychosocial process, delay in treatment initiation and persistent residual symptoms often render a poor prognosis.[2] It is thus important to maximize reinforcement of the treatment effects during acute schizophrenic psychosis to minimize residual symptoms and relapse frequency and to improve functional outcome.

Potentiation of *N*-methyl-D-aspartate (NMDA) receptor–mediated neurotransmission has been proposed as a treatment alternative for schizophrenia.[3] Several studies have demonstrated the clinical benefits of treatment for chronic schizophrenia that targets the glycine site of the NMDA receptor (the NMDA-glycine site). These agents include D-serine,[4] glycine,[5-7] and D-cycloserine.[8,9] D-Cycloserine can reduce negative symptoms.[8,9] D-Serine, D-alanine,[10] and glycine can reduce negative and cognitive symptoms.[4-7] Another approach to enhance NMDA neurotransmission is through increasing the availability of synaptic glycine by the attenuation of glycine reuptake through glycine trans-

porter 1 (GlyT-1). *N*-methylglycine (sarcosine) is a potent endogenous inhibitor of GlyT-1.[11] A recent study[12] suggests that adding sarcosine to stable antipsychotic drug regimens improves the negative and cognitive symptoms of chronically stable schizophrenia. Furthermore, D-serine and sarcosine can improve positive symptoms in patients with chronic schizophrenia taking stable doses of antipsychotic agents.[4,12]

Glycine transporter 1 plays a pivotal role in maintaining the concentration of glycine in synapses at a subsaturating level. Sarcosine is a prototypic compound for GlyT-1 inhibitors, with an inhibition concentration of 50% (IC_{50}) at low micromolar range.[13] Supporting the critical role that GlyT-1 plays in NMDA neurotransmission, *N*[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy) propyl]sarcosine, a sarcosine analogue and a GlyT-1 inhibitor, can enhance NMDA neurotransmission.[14,15] Changes in glycine levels induced by GlyT-1 inhibitors were also observed in vivo.[16] In behavioral studies, the potency of a series of GlyT-1 antagonists for inhibiting phencyclidine-induced hyperactivity in vivo correlated significantly with their potency in antagonizing GlyT-1 in vitro.[17] In rodents, concurrent treatment with *N*[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine prevents the dopaminergic dysregulation observed after phencyclidine administration.[18] In addition, GlyT-1 heterozygous knockout mice are more resistant to the phencyclidine-induced disruption of prepulse inhibition.[19] Also, anatomic distribution of GlyT-1 parallels that of the NMDA receptor.[20]

Previous studies of the NMDA-enhancing agents were all conducted in patients with chronic stable disease. Whether NMDA-enhancing agents benefit acute exacerbation of schizophrenia remains unknown. Moreover, whether a GlyT-1 inhibitor is clinically more effective than an NMDA-glycine site agonist needs to be investigated. Sarcosine may be superior to D-serine by extending its therapeutic effects beyond the core symptoms of schizophrenia; in the trial[12] of patients with chronically stable disease, Positive and Negative Syndrome Scale (PANSS) general subscale scores improved in addition to positive, negative, and cognitive subscale scores. However, this finding requires confirmation in a parallel comparison study. In addition, although sarcosine treatment can be beneficial for patients receiving either typical antipsychotic agents or an atypical agent, risperidone,[12] the effects of D-serine in patients taking risperidone or other newer antipsychotic drugs have not yet been explored. To maximize the treatment effect of acutely exacerbated schizophrenia, we conducted this placebo-controlled efficacy and safety study to compare a GlyT-1 inhibitor, sarcosine, and an NMDA-glycine site agonist, D-serine, while patients received optimal risperidone therapy.

METHODS

PATIENTS

This study was initiated and executed by the investigators in Taiwan. Patients were recruited from the inpatient units of China Medical University and Taipei City Psychiatry Center, which are major medical centers in Taiwan, between January 1, 2000, and July 31, 2003. The research protocol was approved by the institutional review boards of these 2 institutions. All newly hospitalized schizophrenic patients with an acute exacerbation of psychosis were screened and evaluated by the research psychiatrists. The patients are ethnically Han Chinese. The *Structured Clinical Interview for* DSM-IV[21] was conducted for the diagnosis. Patients entered into this study if they (1) were physically healthy and had values that were in the reference range for all the laboratory assessments (including urine and blood routine analyses, biochemical tests, and electrocardiography), (2) were aged 18 to 60 years, (3) satisfied *DSM-IV* criteria for schizophrenia,[22] (4) had a minimum baseline total score of 60 on the PANSS,[23,24] (5) had no *DSM-IV* diagnosis of substance (including alcohol) abuse or dependence, (6) were nonsmokers, (7) had not received depot antipsychotic agents for the preceding 6 months, (8) had no history suggesting that antipsychotic drug treatment would be contraindicated, and (9) had never received atypical antipsychotic drugs. After complete description of the study to the patients, written informed consent was obtained in line with the guidelines of the institutional review boards.

STUDY DESIGN AND INTERVENTION

During the washout period, the participants were administered placebo for up to 7 days, which could be shortened to a minimum of 1 day to protect patients from decompensating psychotic symptoms. All the patients were then randomly assigned under double-blind conditions to receive a 6-week trial of placebo, 2 g of D-serine, or 2 g of sarcosine daily. Patients were randomized in clusters of 6, without stratification, using a computer-generated randomization table to receive placebo or active drug in a 1:1:1 ratio. To ensure concealment of the randomization assignment, medication was provided in coded containers of identical-appearing capsules of placebo or active drug. The research pharmacist implemented random allocation, and masked treatment assignment was communicated by telephone to study staff. Patients, caregivers, and investigators (except the investigational pharmacist) were masked to the assignment. The doses of both amino acids were equivalent to those used in earlier studies[4,12] that were effective for add-on therapy in chronically stable patients. D-Serine and sarcosine were provided by Natural Pharmacia International Inc (Belmont). Purity of more than 99% was confirmed by high-performance liquid chromatography. Placebo, D-serine, and sarcosine were packed with the same additives.

Risperidone therapy was also initiated concurrently for all patients. The dose of this atypical antipsychotic agent was gradually titrated to the target dose of 6 mg/d (or lower in cases of treatment-emergent adverse effects) in the first week. The dose of risperidone could be adjusted on day 14 or on day 28 according to drug adverse effects and clinical assessments (see the "Assessments" subsection). This dosing strategy for risperidone was based on recent studies.[25,26] For acutely exacerbated individuals, the mean end-point dosages in most studies[27-31] were 8 to 12 mg/d; another study[32] used a fixed dose of 6 mg/d. However, in previous studies[25,26] in a similar population we found that the dosing strategy to minimize adverse effects can still yield favorable efficacy. Therefore, we applied the same dosing strategy to obtain the optimal response to risperidone treatment in this study.

Lorazepam treatment was allowed as needed for insomnia or agitation, and benztropine treatment was allowed for extrapyramidal adverse effects. No other centrally acting drugs or cytochrome P450 inducers (or inhibitors) that might interfere with risperidone's metabolism[33] were used. Patient compliance and safety were closely monitored by the research psychiatrists and the inpatient nursing staff.

The sample size was determined on the basis of the earlier studies[4,12] conducted in chronically ill patients. Sixty-five schizophrenic patients were enrolled, and 57 patients completed the double-blind, placebo-controlled study. Three patients in the placebo group, 2 in the D-serine group, and 3 in the sarcosine group discontinued participation after the week 4 assessment owing to nonadherence to the protocol (**Figure 1**). The demographic characteristics of the patients are given in **Table 1**.

ASSESSMENTS

The primary outcome measures were psychopathologic changes measured by total scores on the PANSS[23,24] and the Scales for the Assessment of Negative Symptoms (SANS) (20 and 17 items).[34] The 20-item SANS includes the attention subscale (with 2 items) and the incongruity of affect item. After removing these 3 items (not part of negative symptom construct), the 17-item SANS may better reflect the negative symptom profiles.[34] A secondary analysis explored whether the positive results (if any) from the primary outcome measures were due to a general effect on all subscales or to an effect on a specific subscale.

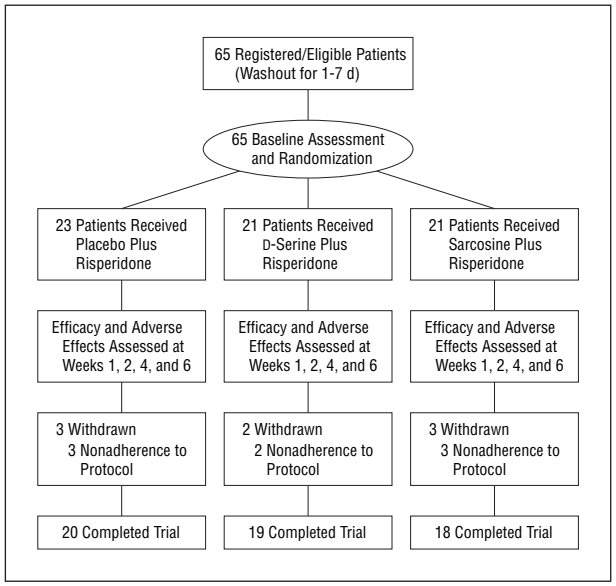

Figure 1. Progress of the 65 patients during the trial.

The original PANSS contains 3 subscales: positive, negative, and general psychiatric symptoms.[23] Further factor analyses, however, revealed 5 components: positive, negative, cognitive, depression, and excitement.[24] The cognitive component consists of 5 items: conceptual disorganization, difficulty in abstract thinking, mannerism and posturing, disorientation, and lack of judgment and insight.[24] In the present study, we thus used the 5 components plus general psychiatric symptoms as the secondary outcome variables for PANSS.

The SANS consists of 5 subscales: blunted affect, alogia, apathy, anhedonia/asociality, and attention. For the assessment of negative symptoms, we a priori chose SANS to avoid multiple comparisons because in the earlier D-cycloserine trial,[8] the SANS seemed to be more sensitive than the PANSS-negative. This strategy for measuring negative symptoms is the same as that used in previous studies of NMDA-enhancing agents.[4,6,8,12] Nevertheless, we also present the findings in PANSS-negative scores. We also a priori defined marked response as a 30% or more reduction in the PANSS total score. The reason we chose such a rigorous criterion is to find a strategy of pharmacotherapy that can produce marked improvement and a better long-term prognosis.

Adverse effect assessments included the Simpson-Angus Rating Scale for extrapyramidal adverse effects,[35] the Abnormal Involuntary Movement Scale for dyskinesia,[36] and the Barnes Akathesia Scale.[37] Systemic adverse effects of treatments were evaluated by means of routine physical and neurologic examinations and laboratory tests and were reviewed by applying the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale.[38]

Clinical ratings were performed by research psychiatrists trained and experienced in the rating scales. Interrater reliability was analyzed using the analysis of variance test. Only raters reaching the intraclass correlation coefficient of 0.90 or higher

Table 1. Demographic, Schizophrenic, and Treatment Characteristics of the 65 Patients Assigned to Receive Placebo, D-Serine, or Sarcosine and Optimal Risperidone Treatment

Characteristic	Study Group: Sarcosine (n = 21)	Study Group: D-Serine (n = 21)	Study Group: Placebo (n = 23)	*P* Value*
Female sex, No. (%)	7 (33)	11 (52)	11 (48)	.43
Age, mean (SD), y	36.1 (10.2)	31.8 (10.4)	34.1 (8.7)	.30
Education level, mean (SD), y	10.6 (3.1)	10.0 (3.0)	10.8 (2.6)	.47
Age at onset of psychosis, mean (SD), y	25.5 (8.7)	24.3 (7.0)	22.6 (6.8)	.32
Hospitalizations, mean (SD), No.	1.8 (1.8)	1.4 (1.7)	1.9 (2.3)	.75
Schizophrenia subtype, No. (%)				
Paranoid	15 (71)	14 (67)	14 (61)	
Disorganized	0	1 (5)	4 (17)	.28
Undifferentiated	6 (29)	6 (29)	5 (22)	
Antipsychotic drug treatment before this hospitalization, No. (%)				.81
Never treated	4 (19)	5 (24)	4 (17)	
Discontinued by patients	13 (62)	10 (48)	15 (65)	.81
Regularly treated	4 (19)	6 (29)	4 (17)	
Placebo lead-in period, mean (SD), d	4.3 (1.9)	3.7 (1.6)	4.2 (1.9)	.38
Risperidone dose, mean (SD), mg				
Day 7	4.0 (1.2)	4.1 (1.0)	3.7 (1.3)	.47
Day 14	4.0 (1.1)	4.1 (1.0)	3.8 (1.3)	.90
Day 28	3.9 (1.2)	4.0 (1.1)	3.9 (1.3)	.51
Day 42	3.7 (1.2)	4.1 (1.2)	3.8 (1.3)	.45

*By Kruskal-Wallis test or χ^2 test as appropriate.

during prestudy training were allowed to rate the study patients. To maintain high interrater reliability and to prevent rater drift, raters met at least once a month for training and reliability retesting. Individual patients were assessed by the same research psychiatrist throughout the trial. Assessments were completed at baseline and at the end of weeks 1, 2, 4, and 6.

STATISTICAL ANALYSES

The demographic and clinical characteristics of the patients, the risperidone doses, and the adverse effects were compared among groups by using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. To assess the efficacy in various clinical domains and to take into account patient effects, mixed-effects models[39] were used (with intercept as the random effects) for all normally distributed outcomes, with main effects for treatment (sarcosine, D-serine, or placebo), time (0, 1, 2, 4, or 6 weeks), and the treatment × time interaction. The significance of treatment effects across time was assessed by the significance of the treatment × time interaction while controlling for the main effects. Unlike analysis of variance, the mixed-effects model does not obtain a statistical value and its *P* value in all groups. In the mixed-effects models, because there are 3 comparison groups, the placebo group was selected to be compared with the other 2 groups.

Because multiple linear regression can be applied only if the distribution of the response values is symmetrical, we examined the distribution patterns of the PANSS and SANS scores using the Kolmogorov D package in SAS/INSIGHT v8.2 (SAS Institute Inc, Cary, NC). For outcome variables with nonnormal distributions, Mann-Whitney tests between pairs of treatments were used. Significance is assessed by comparing endpoint data while controlling for baseline data.

The estimated odds of marked treatment response during the study were analyzed based on multiple logistic regressions. However, because no mixed-effects model is currently available for multiple logistic regressions, the generalized estimating equation[40] method (for fixed-effects models) is used herein. For repeated-measures studies (such as the present one), longitudinal follow-up data obtained from the same patient, however, are intra-individually related and violate the "independent" requirement of multiple linear regression. To adjust this within-subject dependence effect, Zeger et al[40] proposed a generalized estimating equation statistical method for generalized linear models in repeated-measures studies. In this study, the odds ratio of responder status was modeled comparing the placebo and D-serine groups with the sarcosine group after adjustment for time effects and baseline PANSS and SANS total scores. The analysis of the response rate was intent to treat. All hypothesis tests were 2-sided and were conducted at $\alpha = .05$.

RESULTS

The demographic and clinical characteristics of the patients were similar in the 3 groups (Table 1). Of the 65 patients, 13 had never received pharmacotherapy, 38 had discontinued typical antipsychotic drug therapy by themselves before this hospitalization, and 14 had acute exacerbations even while taking typical antipsychotic agents and required a pharmacotherapy change for this study. The frequency distributions were similar among the groups (Table 1). The participants had fewer than 2 inpatient treatments on average. After hospital admission, the duration of the placebo lead-in period and the risperidone doses during the trial were also similar among the groups (Table 1). The symptom severity of the patients was similar to that in the clinical trials[25,26] of schizophrenia with acute exacerbation.

CLINICAL OUTCOMES

Clinical changes in the primary and secondary outcomes are given in **Table 2** and **Table 3**. For the primary outcome measures, in terms of the PANSS performance, the sarcosine group showed better response than the other 2 groups (Table 3). The sarcosine group revealed greater reductions in PANSS-total scores compared with the placebo group ($t = -1.99$; $P = .04$) and the D-serine group ($t = -3.44$; $P < .001$). As for the SANS performance, the sarcosine group was also superior to the other 2 groups (Table 3). Sarcosine adjunctive treatment was superior to placebo in reducing SANS-20 ($t = -2.71$; $P = .007$) and SANS-17 ($t = -2.99$; $P = .003$) total scores and to D-serine in decreasing SANS-20 ($t = -2.78$; $P = .006$) and SANS-17 ($t = -3.08$; $P = .002$) total scores. However, co-administration of D-serine and risperidone was not significantly different from risperidone monotherapy in all of the primary clinical measures (PANSS-total, SANS-20, and SANS-17) (Table 3).

To compare the primary treatment effects among the 3 treatment groups on days 7, 14, 28, and 42, the mixed-effects method was also used (with intercept as the random-effects term to adjust patient effects) to examine the significance of the treatment × time interaction while controlling for the effects of treatment and time. Compared with the placebo group, the sarcosine group showed significantly greater reductions in PANSS total scores on days 14, 28, and 42; in SANS-20 scores on days 14, 28, and 42; and in SANS-17 scores on days 14, 28, and 42. Sarcosine adjunctive treatment also surpassed D-serine use in reducing PANSS total scores at all times; SANS-20 scores on days 14, 28, and 42; and SANS-17 scores at all times (data not shown).

Because there were no significant differences between D-serine and placebo in terms of the primary outcomes, the comparisons in secondary outcomes focused on D-serine vs sarcosine and on placebo vs sarcosine and excluded D-serine vs placebo. For the secondary outcome measures of the PANSS, the sarcosine group had greater reductions than the placebo group in PANSS-general ($t = 3.11$; $P = .002$), PANSS-cognitive ($t = 2.60$; $P = .01$), and PANSS-depression ($t = 2.60$; $P = .01$) scores but not PANSS-positive ($t = -0.17$; $P = .87$) or PANSS-negative ($t = 1.65$; $P = .10$) scores using the mixed-effects models (Table 3). Sarcosine adjunctive treatment also surpassed D-serine in reducing PANSS-general ($t = 3.40$; $P < .001$), PANSS-positive ($t = 2.07$; $P = .004$), PANSS-negative ($t = 3.27$; $P = .001$), and PANSS-depression ($t = 3.41$; $P < .001$) scores but not PANSS-cognitive scores ($t = 1.57$; $P = .12$) (Table 3). The scores in the PANSS-excitement factor, however, were nonnormally distributed and, thus, were unsuitable for traditional regression analyses such as mixed-effects models. Instead, Mann-Whitney tests were used, yielding no significant differences for placebo vs sarcosine and for D-serine vs sarcosine (Table 3).

To compare treatment effects in terms of secondary outcome measures of PANSS on days 7, 14, 28, and 42, respectively, the mixed-effects method was used. Com-

Table 2. Clinical Measures for the 6-Week Placebo-Controlled Sarcosine and D-Serine Trial*

Scale†	Baseline	Week 1	Week 2	Week 4	Week 6
Primary outcomes					
			Placebo Group		
PANSS-total	80.7 ± 10.4	74.6 ± 12.6	68.6 ± 12.7	65.2 ± 12.4	64.1 ± 11.2
SANS-20	38.7 ± 15.4	36.3 ± 16.1	33.8 ± 14.4	31.6 ± 13.3	30.9 ± 12.6
SANS-17	33.5 ± 13.8	32.1 ± 14.4	30.6 ± 13.1	28.9 ± 11.6	28.7 ± 11.4
			Sarcosine Group		
PANSS-total	86.5 ± 11.4	76.4 ± 12.4	69.0 ± 11.6	65.7 ± 12.4	65.1 ± 14.4
SANS-20	45.6 ± 11.9	39.6 ± 12.5	34.8 ± 12.4	32.8 ± 13.4	32.6 ± 14.3
SANS-17	40.4 ± 10.9	36.4 ± 12.3	32.8 ± 12.3	30.7 ± 12.8	29.8 ± 12.8
			D-Serine Group		
PANSS-total	82.2 ± 12.8	79.0 ± 15.5	76.3 ± 16.5	69.3 ± 13.9	68.0 ± 14.4
SANS-20	49.3 ± 21.7	47.8 ± 21.2	46.9 ± 20.7	41.7 ± 19.9	41.8 ± 20.0
SANS-17	42.9 ± 19.5	42.9 ± 18.9	42.0 ± 18.3	38.4 ± 17.8	38.5 ± 17.7
Secondary outcomes					
			Placebo Group		
PANSS-general	34.8 ± 5.3	32.7 ± 6.6	30.1 ± 6.0	28.7 ± 5.9	28.6 ± 4.9
PANSS-positive	13.4 ± 2.8	12.0 ± 3.0	10.7 ± 2.9	9.3 ± 2.7	9.1 ± 2.2
PANSS-negative	19.6 ± 4.2	18.3 ± 5.1	17.3 ± 4.7	17.0 ± 4.7	16.7 ± 4.5
PANSS-cognitive	13.3 ± 3.8	12.6 ± 4.0	12.0 ± 3.8	11.1 ± 3.4	10.8 ± 3.1
PANSS-depression	9.5 ± 1.9	8.9 ± 2.5	8.1 ± 2.1	8.0 ± 2.3	8.0 ± 2.0
PANSS-excitement	7.5 ± 1.9	6.3 ± 2.2	5.4 ± 1.9	5.2 ± 1.6	5.3 ± 1.7
SANS-affect	7.9 ± 5.2	7.5 ± 5.5	7.1 ± 4.5	6.9 ± 4.4	7.1 ± 4.4
SANS-alogia	5.9 ± 4.8	5.7 ± 4.7	5.5 ± 4.3	5.1 ± 3.4	5.2 ± 3.3
SANS-apathy	7.9 ± 3.9	7.3 ± 4.1	6.6 ± 3.8	6.0 ± 3.6	5.5 ± 3.3
SANS-anhedonia	13.1 ± 3.8	12.8 ± 3.9	12.5 ± 4.1	11.7 ± 4.0	11.6 ± 4.1
SANS-attention	3.9 ± 2.7	3.0 ± 2.7	2.0 ± 2.7	1.7 ± 2.5	1.5 ± 2.1
			Sarcosine Group		
PANSS-general	39.8 ± 6.0	33.3 ± 6.2	30.3 ± 5.1	28.9 ± 5.1	29.0 ± 6.2
PANSS-positive	13.4 ± 3.6	11.6 ± 3.2	10.4 ± 3.1	9.7 ± 3.3	9.1 ± 3.7
PANSS-negative	21.3 ± 3.7	19.9 ± 4.8	18.0 ± 4.9	17.3 ± 5.3	16.9 ± 5.0
PANSS-cognitive	14.5 ± 2.6	12.8 ± 2.6	11.5 ± 2.4	10.7 ± 2.3	10.9 ± 2.8
PANSS-depression	11.2 ± 2.3	9.5 ± 2.2	8.6 ± 2.4	8.3 ± 2.2	8.3 ± 2.5
PANSS-excitement	7.7 ± 2.1	6.0 ± 1.7	5.3 ± 1.2	5.1 ± 1.5	5.7 ± 2.7
SANS-affect	12.4 ± 4.9	10.9 ± 4.7	8.9 ± 4.5	8.9 ± 4.8	7.9 ± 4.8
SANS-alogia	7.5 ± 3.7	6.7 ± 3.8	5.7 ± 3.4	4.9 ± 3.5	5.2 ± 3.7
SANS-apathy	8.8 ± 3.6	7.6 ± 3.5	7.0 ± 3.3	6.2 ± 3.3	5.8 ± 3.5
SANS-anhedonia	12.6 ± 3.8	12.0 ± 4.3	11.8 ± 4.7	11.2 ± 4.7	11.4 ± 4.3
SANS-attention	4.2 ± 2.4	2.4 ± 2.1	1.4 ± 2.0	1.6 ± 2.3	2.3 ± 2.2
			D-Serine Group		
PANSS-general	35.7 ± 6.6	34.1 ± 7.5	32.8 ± 7.9	29.6 ± 6.4	28.6 ± 6.4
PANSS-positive	12.0 ± 3.3	11.0 ± 3.0	10.7 ± 3.0	9.5 ± 2.7	9.3 ± 3.0
PANSS-negative	21.0 ± 6.2	21.3 ± 6.3	21.0 ± 6.2	19.0 ± 5.8	19.1 ± 5.9
PANSS-cognitive	15.0 ± 4.7	14.0 ± 4.2	13.4 ± 4.5	12.0 ± 4.3	11.6 ± 4.2
PANSS-depression	9.5 ± 2.4	9.3 ± 2.9	9.0 ± 2.8	8.3 ± 2.1	7.9 ± 2.3
PANSS-excitement	6.8 ± 2.3	6.0 ± 1.9	5.8 ± 2.1	5.1 ± 1.7	4.8 ± 1.5
SANS-affect	15.3 ± 9.6	14.9 ± 9.4	15.2 ± 8.7	13.7 ± 8.2	14.0 ± 8.2
SANS-alogia	8.3 ± 4.8	8.0 ± 4.4	8.0 ± 4.2	7.1 ± 4.0	6.8 ± 4.2
SANS-apathy	8.6 ± 3.9	8.5 ± 3.9	8.0 ± 4.1	7.1 ± 4.3	6.9 ± 3.9
SANS-anhedonia	12.4 ± 3.9	12.6 ± 3.9	12.2 ± 3.7	11.6 ± 3.6	11.7 ± 3.7
SANS-attention	4.7 ± 3.0	3.8 ± 3.0	3.4 ± 2.9	2.3 ± 2.2	2.4 ± 2.5

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SANS, Scales for the Assessment of Negative Symptoms.
*Data are given as mean ± SD.
†See the "Assessments" subsection of the "Methods" section for SANS-20, SANS-17, and the PANSS and SANS subscales.

pared with the sarcosine group, the placebo group showed significantly smaller reductions in PANSS-general psychiatric symptom scores at all assessment points ($P=.01$ for day 7, $P=.004$ for day 14, $P=.004$ for day 28, and $P=.005$ for day 42); in PANSS-negative scores on day 42 ($P=.01$); in PANSS-cognitive scores on days 14 ($P=.005$), 28 ($P=.005$), and 42 ($P=.006$); and in PANSS-depression scores on days 14 ($P=.04$), 28 ($P=.02$), and 42 ($P=.02$), but not in PANSS-positive scores at all points (data not shown). Sarcosine adjunctive treatment also surpassed D-serine in reducing PANSS-general psychiatric symptom scores at all points ($P=.003$ for day 7, $P<.001$ for day 14, $P=.003$ for day 28, and $P=.03$ for day 42), in PANSS-positive scores on days 14 ($P=.009$) and 42

Table 3. Treatment Effects for the 6-Week Placebo-Controlled Sarcosine and D-Serine Trial

Scale*	Sarcosine vs Placebo		D-Serine vs Placebo		Sarcosine vs D-Serine	
	t†	*P* Value	*t*†	*P* Value	*t*†	*P* Value
Primary outcomes						
PANSS-total	–1.99	.04	1.34	.18	–3.44	<.001
SANS-20	–2.71	.007	0.09	.93	–2.78	.006
SANS-17	–2.99	.003	0.17	.87	–3.08	.002

Scale	Placebo vs Sarcosine		D-Serine vs Sarcosine	
	t‡ or *z*§	*P* Value	*t*‡ or *z*§	*P* Value
Secondary outcomes				
PANSS-general	3.11†	.002	3.40†	<.001
PANSS-positive	–0.17†	.87	2.07†	.004
PANSS-negative	1.65†	.10	3.27†	.001
PANSS-cognitive	2.60†	.01	1.57†	.12
PANSS-depression	2.60†	.01	3.41†	<.001
PANSS-excitement	0.56‡	.57	0.22‡	.83
SANS–blunted affect	2.39‡	.02	1.47‡	.14
SANS-alogia	2.98‡	.003	1.66‡	.10
SANS-apathy	1.12‡	.23	1.82‡	.07
SANS-anhedonia	0.45‡	.65	1.77‡	.08
SANS-attention	0.09‡	.93	0.45‡	.66

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SANS, Scales for the Assessment of Negative Symptoms.

*See the "Assessments" subsection of the "Methods" section for SANS-20, SANS-17, and the PANSS and SANS subscales and "Clinical Outcomes" subsections.

†Mixed-effects models (*df* = 249 for all) for the primary outcomes. Placebo is used as the reference group to be compared with the sarcosine and D-serine groups. The comparison between sarcosine and D-serine is derived from another mixed-effects model analysis (*df* = 249 for all) using D-serine as the reference group. Significance is assessed by the treatment × time interaction while controlling for the effects of treatment and time. See also the "Statistical Analyses" and "Clinical Outcomes" subsections.

‡Mixed-effects models (*df* = 249 for all) for the normally distributed secondary outcomes. Sarcosine is used as the reference group to be compared with the other 2 groups.

§Mann-Whitney tests between pairs of treatments for the secondary outcomes with nonnormal distributions. Significance is assessed by comparing end-point data while controlling for baseline data.

(*P* = .04), in PANSS-negative scores at all points (*P* = .004 for day 7, *P* < .001 for day 14, *P* = .002 for day 28, and *P* = .003 for day 42), in PANSS-cognitive scores on day 14 (*P* = .02), and in PANSS-depression scores at all points (*P* = .01 for day 7, *P* < .001 for day 14, *P* = .005 for day 28, and *P* = .03 for day 42).

For the secondary outcome measures of the SANS subscales, the mixed-effects method was unsuitable owing to the asymmetrical distribution of the SANS subscale scores. Therefore, Mann-Whitney tests for placebo vs sarcosine and for D-serine vs sarcosine were performed. Significance was assessed by comparing end-point data while controlling for baseline data. Sarcosine adjunctive treatment was superior to placebo in reducing blunted affect ($z = 2.39$; $P = .02$) and alogia ($z = 2.98$; $P = .003$) scores. No other significant between-group differences were found (Table 3).

Overall, sarcosine-treated patients were more likely to show a marked response (≥30% reduction in the PANSS total score) than the placebo group but not the D-serine group (placebo vs sarcosine: $z = -1.98$; $P = .047$; and D-serine vs sarcosine: $z = -1.46$; $P = .15$) (**Figure 2**). In addition, doses of risperidone at the end of the study did not correlate with the changes in all the outcome measures.

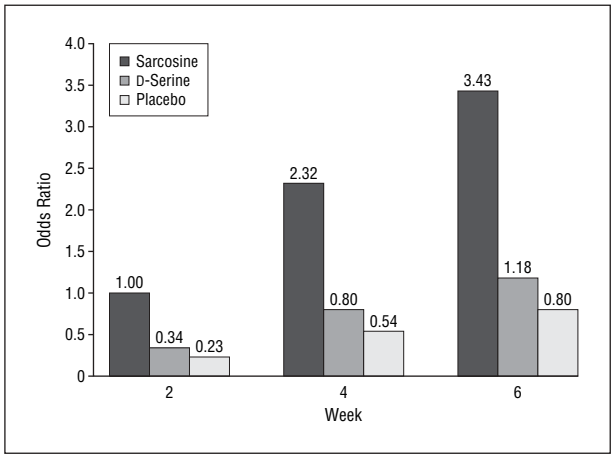

Figure 2. Estimated odds ratio of marked response during the study. The odds ratio was modeled comparing the placebo and D-serine groups with the sarcosine group after adjustment for time effects and baseline total scores on the Positive and Negative Syndrome Scale and the Scales for the Assessment of Negative Symptoms. The response rate was intention to treat. Placebo vs sarcosine: $z = -1.98$; $P = .047$; D-serine vs sarcosine: $z = -1.46$; $P = .15$.

ADVERSE EFFECTS

All 3 treatment groups had minimal extrapyramidal symptoms at the beginning of the study. The mean ± SD baseline scores were similar in the 3 groups on the Simpson-Angus Rating Scale (sarcosine group, 0.4 ± 1.2; D-serine group, 0.4 ± 1.2; and placebo group, 0.1 ± 0.6; $P = .74$), the Abnormal Involuntary Movement Scale (sarcosine group, 0.2 ± 0.9; D-serine group, 0.1 ± 0.4; and placebo group,

Table 4. Adverse Events Other Than Extrapyramidal Symptoms During the Study*

Adverse Event	Patients, No.			
	Sarcosine Group	D-Serine Group	Placebo Group	Total
Weight gain	12	14	14	**40**
Palpitations	4	9	11	**24**
Insomnia	4	4	6	**14**
Fatigability	5	4	3	**12**
Orthostatic dizziness	2	4	4	**10**
Weight loss	3	1	2	**6**
Tension	2	1	2	**5**
Salivation	0	3	2	**5**
Sedation	2	2	0	**4**
Hypersomnia	2	1	0	**3**
Constipation	2	1	0	**3**
Depression	0	1	1	**2**
Others	1	3	2	**6**
Total	**39**	**48**	**47**	**134**

*All *P* values are not significant for comparisons among the 3 study groups. Systemic adverse effects of treatments were reviewed by applying the Udvalg for Kliniske Undersogelser Side Effect Rating Scale.[38]

0.7±1.7; *P*=.87), and the Barnes Akathesia Scale (sarcosine group, 0.3±1.1; D-serine group, 0.1±0.6; and placebo group, 0.1±0.4; *P*=.70). Because our dosing strategy for risperidone was to curtail adverse effects as much as possible,[30,31] the 3 groups revealed only minimal mean±SD extrapyramidal symptoms after treatment and did not have significant differences among the groups (Simpson-Angus Rating Scale: sarcosine group, 0.7±1.5; D-serine group, 0.5±1.2; and placebo group, 0.8+2.4; *P*=.79; Abnormal Involuntary Movement Scale: sarcosine group, 0.6±2.0; D-serine group, 0.0±0.0; and placebo group, 0.2±0.7; *P*=.046; and Barnes Akathesia Scale: sarcosine group, 0.8±1.7; D-serine group, 0.4±1.1; and placebo group, 0.7±2.2; *P*=.53).

Treatment-emergent adverse events other than extrapyramidal symptoms were also similar in the 3 groups (**Table 4**). These systemic adverse effects were all short-lived and did not warrant medical treatment. Routine blood cell counts, chemistry test results, and electrocardiographic findings after treatment remained unchanged and were all within the reference ranges (data not shown). No dropout was due to adverse effects.

Three patients in the sarcosine group, 4 in the D-serine group, and 2 in the placebo group received lorazepam for agitation during the trial (χ^2=0.99; *P*=.61). At the end point, 9 patients in the sarcosine group, 11 in the D-serine group, and 12 in the placebo group received lorazepam for insomnia (χ^2=0.50; *P*=.77), and 3 patients in the sarcosine group, 4 in the D-serine group, and 4 in the placebo group received benztropine for extrapyramidal adverse effects (χ^2=0.18; *P*=.91). The mean±SD end-point dosages of lorazepam (0.6±1.0 mg/d in the sarcosine group, 0.8±0.9 mg/d in the D-serine group, and 1.1±1.2 mg/d in the placebo group) or benztropine (0.6±2.2 mg/d in the sarcosine group, 0.5±1.4 mg/d in the D-serine group, and 0.4±1.0 mg/d in the placebo group) did not differ significantly among groups either.

COMMENT

To our knowledge, this is the first study of the use of NMDA-enhancing agents for patients with acutely symptomatic schizophrenia. Our findings indicate that sarcosine, a GlyT-1 inhibitor, when combined with risperidone, can exert synergistic benefits for negative and other psychiatric symptoms in acutely symptomatic schizophrenia. In contrast, risperidone plus D-serine did not differ significantly from risperidone alone in the short-term treatment. Together with recent studies,[4,12] the present study suggests that sarcosine can benefit not only patients with long-term stable disease but also acutely ill persons with schizophrenia (Tables 2 and 3 and Figure 2). However, D-serine at a dosage of 2 g/d is efficacious only for patients with long-term stable disease.

Acute exacerbation of schizophrenia is a common clinical challenge. The therapeutic approach of dopamine subtype II receptor/serotonin subtype II receptor (D_2/$5HT_2$) antagonists plus NMDA-enhancing agents can provide additional benefits not only for symptom reduction during the acute phase but also for the possibility that schizophrenic psychosis can be a detrimental biopsychosocial process.[2] However, clinicians should not treat patients with these agents until investigational trials are completed.

To date, few data are available for comparisons among NMDA-enhancing agents.[41] We compared the 2 NMDA receptor–enhancing agents sarcosine and D-serine in a 6-week add-on design. The results suggest that GlyT-1 may be a more effective target to enhance NMDA function than the NMDA-glycine site. This difference may be due to the fact that sarcosine acts by blocking the re-uptake of released glycine, whereas NMDA-glycine site agonists tonically stimulate the receptor. Also, transporter inhibitors may be more efficacious than the transmitter itself. Similarly, serotonin transporter inhibitors are superior to tryptophan (a neurotransmitter precursor, albeit not a neurotransmitter) for the treatment of depression.[42] We compared only 1 dose of D-serine and sarcosine; higher doses of D-serine may be needed to activate the NMDA receptor to curtail the acute schizophrenia psychosis than for the chronic symptoms. In addition, the negative symptoms of the acutely exacerbated patients in this study were not as severe as those in the previous studies for chronically ill patients. The limited level of negative symptoms at baseline may also help explain the limited negative symptom response in the D-serine group.

The pharmacokinetic interaction of sarcosine or D-serine with risperidone is unclear. The greater efficacy of sarcosine can be due to a favorable kinetic interaction between sarcosine and risperidone. However, the optimal doses of risperidone were similar across the 3 treatment groups, and the risperidone doses used to achieve optimal response in the study of acute schizophrenia were similar to those used in the study of chronic stable disease.[12] Furthermore, there is no correlation between the risperidone doses and any outcome measure in the sarcosine group. It is, therefore, unlikely that the synergistic effect of sarcosine is due to a pharmacokinetic effect on risperidone.

For chronically ill schizophrenic patients, add-on sarcosine treatment, similar to D-serine treatment, im-

proves positive and negative symptoms for patients receiving stable doses of risperidone.[4,12] A recent study[7] of high-dose glycine treatment (0.8 g/kg per day) also suggests that glycine can improve positive symptoms in patients stabilized with risperidone or clozapine. However, for acutely symptomatic patients in the present study, sarcosine and D-serine did not yield extra benefits for positive symptoms when combined with optimal risperidone therapy. The limited sample size may contribute to the lack of positive symptom effect of sarcosine in the present study. In addition, the negative finding in the present short-term treatment study can be due to the patient difference from the long-term study.[12] The patients in this short-term study had only approximately 2 inpatient treatments. However, in the long-term patient study,[12] we selected a group whose positive symptoms did not respond well to antipsychotic drug therapy. In contrast, the short-term study patients may have responded to risperidone alone, and a "floor effect" can prevent further improvement by the NMDA agents.

The NMDA neurotransmission regulates synaptic plasticity, memory, and cognition.[43] This cognition-enhancing effect is also supported by the positive findings of a D-serine study,[4] which applied the Wisconsin Card Sorting Test. Consistent with this, patients taking sarcosine improved significantly in their cognitive symptoms as measured by the PANSS (see the definition in the "Assessments" subsection of the "Methods" section) (Table 3), as in the D-serine trial and the 2 glycine trials[6,44] in long-term patients. Nevertheless, cognitive function as inferred by the neuropsychologic testing of various attention, memory, executive, and information-processing functions needs to be studied in detail before any conclusion can be drawn for the therapeutic effect of NMDA-enhancing agents on cognitive function and long-term functional outcome.

In patients with long-term stable schizophrenia, sarcosine,[12] compared with NMDA-glycine site agonists,[5,7,8,11,45] showed additional therapeutic effects beyond the core symptoms of schizophrenia; the PANSS-general symptoms improved too. Although recent studies demonstrated that high-dose glycine treatment (0.8 g/kg per day) can also decrease the PANSS-general subscale score,[41] the present study, with a head-to-head comparison design, lends support to the notion that sarcosine may be superior to NMDA-glycine site agonists in this domain. Earlier, high-dose glycine treatment, compared with placebo, also resulted in a significant reduction in PANSS-depressive scores in patients with treatment-resistant schizophrenia.[6] The results of the present study further suggest that sarcosine may exert better efficacy for depressive symptoms in acutely ill patients with schizophrenia than not only placebo but also D-serine. However, more studies with higher doses of D-serine or other agents, such as glycine or D-cycloserine, are required to confirm that the GlyT-1 agent is in fact superior to NMDA-glycine site agonists.

In patients with long-term stable disease, sarcosine or D-serine did not worsen the adverse effects of other antipsychotic agents, which are mediated by D_2, 5-HT_2, histamine, and muscarinic receptors.[4,12] The present study replicated these findings. The few adverse effects reported by patients were minimal, resolved spontaneously, and did not differ significantly among groups.

Sarcosine is a naturally occurring amino acid in humans. The toxicologic properties of sarcosine have not been thoroughly investigated. Sarcosine dehydrogenase is a mitochondrial matrix flavoenzyme expressed in brain and liver to demethylate sarcosine.[46] The enzyme is defective in patients with sarcosinemia, a rare autosomal metabolic defect characterized by elevated levels of sarcosine in blood and urine. Supporting the safety of using sarcosine as a long-term therapeutic agent of enhancing NMDA neurotransmission, sarcosinemia is generally benign,[46,47] and the phenotype of sarcosine dehydrogenase mutant mice is unremarkable.[48] However, the GlyT-1 homozygous knockout mice do not survive.[19] It was suggested that the complete blockade of GlyT-1 is toxic for rodent development owing to the excessive inhibitory glycinergic drive to the respiratory neurons.[49] A thorough human toxicology study, therefore, is necessary. In rodents, D-serine selectively damages renal proximal tubule cells.[50] In humans, toxicologic profiles of D-serine, however, have not been fully understood. However, D-serine at a dose of 30 mg/kg was not toxic to patients with chronic schizophrenia in the previous trial.[4] The species difference in renal toxicity can be due to the high D–amino acid activity in the rodent kidney, which generates hydrogen peroxide and hydroxyl radicals.[51]

CONCLUSIONS

The present study was limited by its sample size and a fixed-dose comparison without dose-finding trials. The definitive effects of GlyT-1 inhibitors vs NMDA-glycine site agonists and their clinical application require further studies. However, this study indicates that sarcosine, a GlyT-1 inhibitor, may be more efficacious than NMDA-glycine site agonists for adjuvant treatment of schizophrenia, at least during the acute phase. The evidence most strongly supports the benefit of sarcosine for general psychiatric symptoms and depression and a possible benefit for negative symptoms (blunted affect and alogia) but not for positive symptoms during the acute phase. Potentiation of NMDA neurotransmission by the inhibition of GlyT-1 may represent a novel therapeutic approach that is worthy of further investigation. Maximization of pharmacotherapeutic effects during acute psychosis of schizophrenia can be achieved by combination treatment with atypical antipsychotic drugs and the GlyT-1 inhibitor.

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