Sarcosine Therapy for Obsessive Compulsive Disorder

A Prospective, Open-Label Study

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Background: Several lines of evidence implicate glutamatergic neurotransmission in the pathophysiology of obsessive compulsive disorder (OCD). Sarcosine is an endogenous antagonist of glycine transporter-1. By blocking glycine uptake, sarcosine may increase the availability of synaptic glycine and enhance *N*-methyl-D-aspartate (NMDA) subtype glutamatergic neurotransmission. In this 10-week open-label trial, we examined the potential benefit of sarcosine treatment in OCD patients.

Method: Twenty-six outpatients with OCD and baseline Yale-Brown Obsessive Compulsive Scale (YBOCS) scores higher than 16 were enrolled. Drug-naive subjects (group 1, n = 8) and those who had discontinued serotonin reuptake inhibitors for at least 8 weeks at study entry (group 2, n = 6) received sarcosine monotherapy. The other subjects (group 3, n = 12) received sarcosine as adjunctive treatment. A flexible dosage schedule of sarcosine 500 to 2000 mg/d was applied. The primary outcome measures were Y-BOCS and Hamilton Anxiety Inventory, rated at weeks 0, 2, 4, 6, 8, and 10. Results were analyzed by repeated-measures analysis of variance.

Results: Data of 25 subjects were eligible for analysis. The mean ± SD Y-BOCS scores decreased from 27.6 ± 5.8 to 22.7 ± 8.7, indicating a mean decrease of 19.8% ± 21.7% ($P = 0.0035$). Eight (32%) subjects were regarded as responders with greater than 35% reduction of Y-BOCS scores. Five of the responders achieved the good response early by week 4. Although not statistically significant, drug-naive (group 1) subjects had more profound and sustained improvement and more responders than the subjects who had received treatment before (groups 2 and 3). Sarcosine was tolerated well; only one subject withdrew owing to transient headache.

Conclusion: Sarcosine treatment can achieve a fast therapeutic effect in some OCD patients, particularly those who are treatment naive. The study supports the glycine transporter-1 as a novel target for developing new OCD treatment. Large-series placebo-controlled, double-blind studies are recommended.

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PL Wu and HS Tang contributed equally to this work. Wu, Tang, and GE Tsai designed the study, wrote the protocol, analyzed data, and drafted the manuscript. Lane designed the study and drafted the manuscript. CA Tsai participated in the study design and analyzed data. All authors contributed to and have approved the final manuscripts.

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Obsessive compulsive disorder (OCD) is a common psychiatric disorder affecting 2% to 3% of the population.[1] Obsessive compulsive disorder is frequently a chronic debilitating condition. Subjects with OCD often respond inadequately to currently available pharmacotherapy or exposure-based psychotherapy.[2]

Although the clinical experience and research of OCD have mostly focused on the serotonergic systems, convergent lines of evidence have implicated the role of glutamatergic neurotransmission,[3–7] including *N*-methyl-D-aspartate (NMDA) subtype receptor function,[5,7] in the pathophysiology and treatment of OCD (see Ting and Feng[5] for a review of glutamatergic dysfunction in OCD). Preliminary case reports and case series showed that resistant OCD symptoms may benefit from adjunctive nonselective glutamatergic inhibitors such as riluzole,[6,8,9] topiramate,[10] and lamotrigine.[11,12] In preliminary study, memantine, a weak uncompetitive NMDA receptor (NMDAR) antagonist, proved to be efficacious as add-on treatment to resistant OCD.[13,14] Meanwhile, Greenberg et al[7] conducted a randomized trial using glycine, a co-agonist for the activation of NMDAR complex,[15,16] as adjunctive treatment for refractory OCD. There seemed to be a trend favoring glycine treatment. D-cycloserine (DCS), a partial agonist acting on NMDAR coagonist site, has been used to facilitate cognitive behavior therapy for OCD with positive results.[17–19] However, the administration of DCS is intermittent, immediately before each exposure session. Taken together, it is not clear why both nonspecific glutamate inhibitors (or a weak uncompetitive NMDAR antagonist) and NMDA agonist/partial agonist as add-on treatment may benefit patients with OCD.[7,20]

There are rationales for treating OCD by the enhancement of NMDAR-mediated neurotransmission. First, although OCD has been associated with increased activity in frontal-subcortical circuits,[21] it may not indicate a global increase in glutamatergic function. For example, Rosenberg et al[4] have reported reduced glutamatergic concentrations in the anterior cingulate gyrus in drug-naive pediatric patients with OCD. Furthermore, there have been functional and anatomical distinctions of NMDA neurotransmission in the frontal-subcortical circuits that are involved in OCD. For example, either glycine or D-serine selectively increases NMDAR-mediated excitatory postsynaptic currents in dorsolateral rather than in ventromedial striatum.[22] Finally, preclinical studies indicate that potentiation of NMDAR function may reverse NMDAR antagonists–induced pathological glutamate efflux in the hippocampus and prefrontal cortex,[23–25] whereas NMDAR antagonist MK-801 exacerbated repetitive climbing and leaping behavior in a transgenic D1CT-7 mouse model of comorbid Tourette syndrome and OCD.[20] G72/G30 is a presumed D-amino acid oxidase (DAAO) activator.[26] G72 transgenic mouse also showed compulsive behavior.[27]

Because glycine transporter-1 (GlyT-1) regulates and maintains subsaturating concentration of glycine at the coagonist site of NMDARs, several GlyT-1 inhibitors have been developed to enhance NMDA neurotransmission in animal models.[15,16] Sarcosine (*N*-methylglycine), a naturally occurring inhibitor of the GlyT-1, may increase the availability of synaptic glycine near NMDARs.[15,16] Sarcosine has been shown to improve symptoms in schizophrenia, with good tolerability and safety.[28,29] Herein, we conducted this 10-week open-label trial to examine the potential benefit of sarcosine treatment in OCD patients.

METHOD

Subjects

From August 2006 to October 2008, a total of 26 patients with OCD (9 women and 17 men) aged between 19 and 62 years (mean ± SD, 30.3 ± 9.9 years) gave written informed consent for participation in the study. The institutional review board at China Medical University Hospital and Taipei City Hospital approved the study. Potential subjects were diagnosed with primary OCD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria. Inclusion criteria were at least 1-year duration of OCD symptoms and a minimum severity score of 16 or higher on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[30] at screening and at start of sarcosine treatment. Subjects were not included if they had the following: (1) a history of bipolar disorder, schizophrenia, schizoaffective disorder, or other psychosis as defined by *DSM-IV*; (2) moderate to severe depression defined by a 21-item Hamilton Depression Rating Scale (HAM-D)[31] score higher than 17 at the screening visit, (3) any clinically significant systemic disease.

The sample comprised 3 subgroups. Group 1 patients (n = 8) were drug naive at study entry. Group 2 patients (n = 6) had been treated with serotonin reuptake inhibitors (SRIs) but were free from psychotropic medication for at least 8 weeks before study entry. Group 3 patients (n = 12) had inadequate response to their ongoing psychotropic medications at study entry and received add-on sarcosine (Table 1). Inadequate response was defined by a Y-BOCS score higher than 16 despite treatment with maximum tolerated dose of an SRI medication for at least 8 weeks.

TABLE 1. Characteristics of Patients With Obsessive Compulsive Disorder Receiving Sarcosine Treatment

Group	Patient No.	No. Previous Medication Trials	Previous Courses of SRI Trials and Augmentations (mg/d)	Current SRIs	Daily Dose (mg/d)
1	1*	0	x	x	0
	2*	0	x	x	0
	3†	0	x	x	0
	4*	0	x	x	0
	5	0	x	x	0
	6*	0	x	x	0
	7	0	x	x	0
	8†	0	x	x	0
2	9	1	Sertraline 50	x	0
	10	1	Fluoxetine 60	x	0
	11	2	Fluoxetine 40, paroxetine 40	x	0
	12*[a]	1	Fluoxetine 20	x	0
	13	1	Fluoxetine 60	x	0
	14	1	Fluoxetine 60	x	0
3	15	2	Sertraline 200	Sertraline	200
	16	3	Sertraline 200	Fluoxetine	80
	17*	1	Venlafaxine150, fluoxetine 60	Fluoxetine	40
	18	4	Clomipramine100, amitriptyline 125, fluoxetine 60, olanzapine10	Imipiramine	100
	19*[a]	2	Fluoxetine 60, escitalopram 20	Escitalopram	20
	20	2	Fluoxetine 80	Citalopram	40
	21	1	Fluoxetine 60	Fluoxetine	40
	22*	1	Fluoxetine 60	Fluoxetine	60
	23	1	x	Fluvoxamine	150
	24	3	Fluvoxamine 150, fluoxetine 80	Citalopram	60
	25	5	Fluoxetine 60, citalopram 60, fluvoxamine 200, clomipramine 125, venlafaxine 225	Venlafaxine	225
	26[a]	2	Sertraline 150, fluoxetine 60	Fluoxetine	60

Pre–Y-BOCS scores are scores at week 0; Post–Y-BOCS scores are scores at the end of week 10 of sarcosine treatment.

*Responders to sarcosine therapy with change in Y-BOCS greater than 35%.

†Responders to sarcosine therapy with change in Y-BOCS greater than 25% but less than 35% respectively.

[a]Signifies dropout.

Study Design

The study duration was 10 weeks. All the subjects did not concurrently receive behavioral therapy. Group 3 subjects continued their psychotropic medications, but no patients in any group started additional psychotropic medications, except for lorazepam (a maximum of 2 mg/d) or zolpidem (10 mg/d). Sarcosine was started at 500 mg/d. All patients were scheduled for biweekly evaluation at week 0, 2, 4, 6, 8, and 10 with Y-BOCS, and at baseline/end point with Hamilton Anxiety Inventory (HAM-A)[32] and HAM-Depression Rating Scale. The dose can be increased by 500 mg biweekly if there was no decline in Y-BOCS scores compared to the last visit, up to a maximum of 2000 mg/d. Clinical response was defined as a decline of more than 35% of the initial Y-BOCS score.

Measures and Analyses

The efficacy measures, including the Y-BOCS, HAM-A, and Clinical Global Impression-Severity scores, were obtained from 2 researchers who have interrater reliability of greater than 0.85. Data were analyzed for patients with at least one assessment after baseline. Treatment response was analyzed in 2 different ways: (1) with repeated-measures analysis of variance for continuous variables; and (2) χ^2 tests for dichotomous variables. To assess treatment effect of sarcosine over time among different groups, we first determined the best model fit for the relationship among each outcome measure, with group as a between-subjects factor and time as a within-subjects factor.

RESULTS

The entire sample's mean ± SD scores at baseline were 27.6 ± 5.8 for Y-BOCS, 11.0 ± 3.4 for HAM-D, and 19.2 ± 7.7 for HAM-A. The mean ± SD age of onset was 20.0 ± 8.7 and the mean ± SD duration of illness was 9.8 ± 7.3 years. Twelve of the 26 included subjects had comorbid major depressive disorder or dysthymic disorder. The mean ± SD numbers of previous and current trials with antidepressants for OCD were 1.2 ± 0.4 in group 2 and 2.2 ± 1.3 in group 3. Previous SRI trials, history of augmentation strategies, dosage of concomitant medications, and measurements of outcome variables are listed in Table 1.

Although there were no differences in comorbidity, sex, and baseline Y-BOCS, HAM-A, and HAM-D scores among the 3 groups of patients, compared with groups 1 and 3, the subjects

Concomitant Medications (mg/d)	Sarcosine Daily Doses (mg)	Pre–Y-BOCS Scores	Post–Y-BOCS Scores	Pre–HAM-D Scores	Post–HAM-D Scores	Pre–HAM-A Scores	Post–HAM-A Scores
x	1000	26	8	7	4	14	7
x	1000	24	10	16	9	22	11
x	2000	29	21	16	9	30	17
x	500	20	10	10	5	8	7
x	1500	27	24	7	10	23	14
x	1000	30	16	13	2	21	8
x	2000	38	36	13	14	30	23
x	1000	20	14	4	2	8	4
x	2000	17	16	8	7	18	18
x	2000	29	29	12	12	19	20
x	2000	24	23	10	10	16	14
x	1000	25	10	10	5	30	12
x	1000	28	23	6	4	9	8
x	1500	29	26	14	7	19	13
Risperidone 1	2000	35	33	15	13	22	20
x	2000	33	33	5	5	14	14
x	1000	26	16	13	10	19	14
Valproic acid 600	2000	16	13	12	8	13	9
x	500	21	3	7	2	16	5
x	2000	34	34	14	10	33	18
x	2000	26	26	11	7	24	11
Haloperidol 2, alprazolam 0.5	1000	34	19	9	3	15	3
x	2000	31	29	17	11	27	19
Risperidone 1, rivotril 0.5	2000	29	26	8	8	8	7
Valproic acid 1000, lodopine 100	2000	36	35	12	12	31	30
Risperidone 1	500	29	x	14	x	20	x

in group 2 had marginally earlier age (year) of illness onset (19.4 ± 6.6, 15.8 ± 4.8, and 22.6 ± 8.7 for groups 1, 2, and 3, respectively; $P = 0.2$) and were younger at study entry (27.6 ± 6.3, 24.8 ± 5.2, and 34.8 ± 12.0 years of age for groups 1, 2, and 3, respectively; $P = 0.086$).

Twenty-three patients completed the trial. Three subjects dropped out, and two of them were rated as treatment responders (Table 1). Patient 12 dropped out at the fourth week because of being recruited for military service. Patient 19 dropped out at the end of week 2 owing to the emergence of hypomanic symptoms. His hypomanic symptoms remitted 3 days after he stopped taking sarcosine and escitalopram. Patient 26 dropped out because of treatment-related headache. Her headache remitted 1 day after the cessation of sarcosine treatment. Except for patients 19 and 26, sarcosine was generally well tolerated, and no adverse events were noted.

The patients received 1520 ± 549 mg/d of sarcosine at the end of the study. The mean scores decreased over time from 27.6 ± 5.8 to 22.7 ± 8.7 for Y-BOCS (−19.8 ± 21.7%; F = 3.86, $P = 0.0035$) and from 19.2 ± 7.7 to 13.0 ± 7.0 for HAM-A (−31.6 ± 24.9%; F = 6.12, $P = 0.0025$). Four (50%) of group 1 subjects were rated as responders (range, 46.7%–69.2% reduction in Y-BOCS), whereas only 1 (16.7%) of group 2 (patient 12, 60% reduction in Y-BOCS) and 3 (25%) of group 3 patients (38.5, 85.7, and 44.1% reduction in Y-BOCS) were responders (Table 1).

Analyses with repeated-measures analysis of variance showed no significant difference in the reduction of Y-BOCS and HAM-A scores among groups 1, 2, and 3 patients ($P = 0.56$ and $P = 0.21$, respectively). However, group 1 (drug naive) subjects had consistent reduction in Y-BOCS over time (Fig. 1), with effect size quickly reaching 0.8 at week 2 of sarcosine treatment and reaching effect size of 1.56 at the end of the study (Fig. 1). Hamilton Anxiety Inventory scores show similar pattern as Y-BOCS (data not shown). For final responders (n = 8), mean ± SD Y-BOCS scores significantly declined by 11.1 ± 5.6 at week 2, with effect sizes of 2.0, and 5 of them (63%) met the criteria of response within 4 weeks of sarcosine treatment.

Of the demographic variables of age, sex, age of onset, duration of illness, comorbid diagnoses, pretreatment scores of Y-BOCS and HAM-D examined, the shorter duration of illness (6.3 ± 2.6 vs 12 ± 8.2 years; $P = 0.02$) and the later onset of illness (24.1 ± 8.8 vs 17.2 ± 5.0 years old; $P = 0.015$) predicted final response to sarcosine treatment.

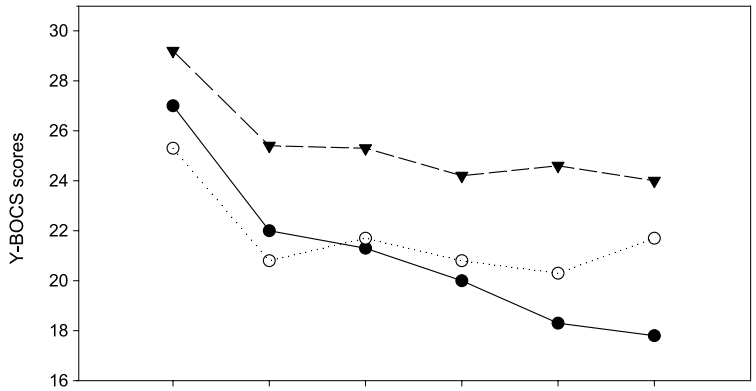
DISCUSSION

We found that sarcosine treatment for 10 weeks significantly reduced the Y-BOCS scores in patients with OCD. Our findings give promise to the development of novel pharmacological treatment for OCD through the modulation of NMDA neurotransmission by GlyT-1 inhibition and substantiate beneficial effects of NMDA-enhancing agent for OCD. Sarcosine treatment may be the best for drug-naive (group 1) subject; 50% of them responded to sarcosine treatment, and 75% of them had more than 25% decrease in Y-BOCS scores. At the same time, the response rates in the other 2 groups are much less than the naive group.

Greenberg et al[7] conducted a double-blind randomized trial investigating the efficacy of glycine as adjunctive treatment for OCD. There was a trend favoring the efficacy of glycine in reducing Y-BOCS score despite high dropout rate for both groups. There is in vitro evidence that sarcosine may act not only as a GlyT-1 inhibitor but also directly as a coagonist of NMDARs at the glycine-binding site.[33] In addition, sarcosine is different from glycine in that, as an NMDAR coagonist, the former had less NMDAR desensitization than the latter.[33]

Sarcosine seemed to have more favorable tolerability than SRIs or glycine concerning the latter's adverse effects of nausea or disagreeable taste. Patient 12, for example, despite fluoxetine at 40 to 60 mg/d, has had moderately improved his pathological doubts and magical thinking; the common fluoxetine-associated sexual dysfunction had aggravated his pathological doubt with sexual dysfunction and mental rituals of undoing the worry on sexual dysfunction. Thus, he refused SRI treatment and requested continuing the sarcosine therapy after the study.

Although the open-label study designs of 3 different populations and small sample size are not optimal, this is a naturalistic study in which we preferred not to stop SRIs in the subjects



	baseline	week 2	week 4	week 6	week 8	week 10	ES
—●— Group 1	27.0 (5.9)	22.0 (8.4)	21.3 (8.2)	20.0 (9.4)	18.3 (9.6)	17.8 (9.5)	−1.56
…○… Group 2	25.3 (4.6)	20.8 (7.3)	21.7 (7.8)	20.8 (7.1)	20.3 (7.1)	21.7 (7.5)	−0.68
—▼— Group 3	29.2 (6.1)	25.4 (10.8)	25.3 (10.5)	24.2 (10.1)	24.6 (9.8)	24.0 (10.4)	−0.74

FIGURE 1. Reduction in the scores of Y-BOCS in 3 groups of patients with obsessive compulsive disorder. Group I, drug naive; group 2, previous SRIs treatment; group 3, ongoing SRI treatment. Analysis of variance time × group; $P = 0.026$. ES indicates Cohen D effect size.

who were taking them to avoid possible flare up of symptoms. Indeed, the response of some of the more refractory patients in groups 2 and 3 is possibly more meaningful, as these are the ones who are likely to have the least placebo response. Patients in group 2 have marginally earlier onset of illness and have stopped their SRIs treatment; in most cases, this is a marker of treatment failure, and so this group can be characterized as poor treatment responder. Therefore, the smaller response to sarcosine in this group is reasonable. Group 3 comprised patients who remained on their SRIs, presumably contains significant fraction of partial SRI responders. They are, therefore, more likely to respond, a priori, than group 2 and less likely than group 1. Nevertheless, the relationship between the effects of sarcosine and SRI's treatment and its response history needs to be elucidated by future stratified placebo-controlled double-blind studies.

Distinct NMDA modulating agents may have pharmacologically, regionally, and temporally differential effects in the frontal-striatal circuitry relevant to OCD. *N*-methyl-D-aspartate receptors containing the NR2A subunit have the highest affinity for competitive antagonists,[34] whereas NMDARs containing the NR2B subunit have greater affinity for agonists such as glycine and D-serine.[34,35] Polymorphism of NR2B subunit gene GRIN2B was associated with vulnerability to OCD.[36] SAP90/PSD95-associated protein 3 gene–deleted mouse has decreased NR2A/NR2B ratio in the striatum and expresses OCD-related phenotype.[37] Synaptic processing of excitatory input is different in the ventromedial and dorsolateral striatum; either glycine or D-serine increases the peak current of NMDAR-mediated excitatory postsynaptic currents selectively in dorsolateral striatum.[22] Nevertheless, the questions remain why (1) sarcosine, as an NMDA enhancer, and memantine, a partial NMDAR antagonist, were both effective in patients with OCD; (2) 63% of the final responders met clinical response within 4 weeks of sarcosine treatment, which is quicker than the onset of response with SRI in OCD.[38]

This study is limited in its open-label design, relatively small sample, and concurrent treatment with psychotropic medications in the add-on group. Despite these limitations, the low dropout rate, significant improvement in Y-BOCS scores, and overall favorable tolerability suggest that sarcosine is of clinical benefit to the patients with OCD. The efficacy of sarcosine in this study adds to the literature implicating that the role glutamatergic neurotransmission plays in the pathophysiology of OCD and GlyT-1 may be a novel therapeutic target for OCD treatment.

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AUTHOR DISCLOSURE INFORMATION

Sarcosine is protected by US patents 6228875, 6667297, 6420351, and 6974821 for which GE Tsai is an inventor. All other authors reported no biomedical financial interests or potential conflicts of interest.

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