ORIGINAL ARTICLE

# Augmentation of Exposure Therapy With D-Cycloserine for Social Anxiety Disorder

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**Context:** Social anxiety disorder (SAD) is common and debilitating. Although exposure therapy is one of the most effective forms of psychotherapy for this disorder, many patients remain symptomatic. Fear reduction in exposure therapy is similar to extinction learning, and early clinical data with specific phobias suggest that the treatment effects of exposure therapy for SAD may be enhanced with D-cycloserine, an agonist at the glutamatergic *N*-methyl-D-aspartate receptor.

**Objective:** To determine whether short-term treatment with 50 mg of D-cycloserine enhances the efficacy of exposure therapy for SAD.

**Design:** Randomized, double-blind, placebo-controlled augmentation trial examining the combination of D-cycloserine or pill placebo with exposure therapy for SAD.

**Setting:** Patients were self-referred from the general community to 1 of 3 research clinics.

**Participants:** Twenty-seven participants meeting *DSM-IV* criteria for SAD with significant public speaking anxiety.

**Interventions:** Following a diagnostic interview and pretreatment assessment, participants received 5 therapy sessions delivered in either an individual or group therapy format. The first session provided an introduction to the treatment model and was followed by 4 sessions emphasizing exposure to increasingly challenging public speech situations with videotaped feedback of performances. One hour prior to each session, participants received single doses of D-cycloserine or placebo.

**Main Outcome Measures:** Symptoms were assessed by patient self-report and by clinicians blind to the randomization condition before treatment, after treatment, and 1 month after the last session.

**Results:** Participants receiving D-cycloserine in addition to exposure therapy reported significantly less social anxiety compared with patients receiving exposure therapy plus placebo. Controlled effect sizes were in the medium to large range.

**Conclusion:** The pilot data provide preliminary support for the use of short-term dosing of D-cycloserine as an adjunctive intervention to exposure therapy for SAD.

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SOCIAL ANXIETY DISORDER (SAD) is a common psychiatric disorder with a lifetime prevalence of 13.3%,[1] making it the third most common psychiatric condition in the United States behind major depression and alcohol abuse. If untreated, the disorder typically follows a chronic, unremitting course leading to substantial impairments in vocational and social functioning.[2-8] Of all social situations, public speaking is the most prevalent fear among individuals with SAD as well as in the general population.[7,9,10]

Numerous outcome trials have demonstrated efficacy for pharmacotherapy (eg, paroxetine hydrochloride, fluoxetine hydrochloride, and phenelzine sulfate) and cognitive behavioral therapy (CBT).[2,11-14] The most efficacious forms of CBT appear to be exposure therapy with or without cognitive intervention.[12,15,16] Despite these advances in treatment, many patients remain symptomatic after initial intervention. For example, Otto et al[17] reported that only 25% of the patients treated with CBT and 20% of those receiving clonazepam met remission criteria at the endpoint. In a study[13] comparing CBT and phenelzine sulfate, 42% of patients receiving CBT and 35% of those receiving phenelzine sulfate improved less than moderately at 12 weeks in the intent-to-treat analysis.

Attempts to boost treatment response with combined CBT and pharmacotherapy have led to disappointing results.[18,19] For example, in a large 2-site trial, Davidson et al[2] found less than a 3% improvement in response rates for the addi-

tion of fluoxetine hydrochloride to CBT; patients with SAD treated with CBT demonstrated a response rate of 51.7%, compared with a response rate of 54.2% for CBT plus fluoxetine hydrochloride. Recently, however, a novel strategy has emerged for the combination of pharmacotherapy and CBT. This strategy is the result of research studies[20-22] that have mapped some of the core pathways and neurotransmitters involved in fear extinction. Fear learning and extinction are both blocked by antagonists at the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor, which is critically involved in learning and memory. D-Cycloserine (DCS), an analogue of D-alanine and a partial agonist at the NMDA receptor, appears to augment learning in animals and in some human trials.[23,24] Moreover, the process of extinction of conditioned fear is facilitated by DCS received in individual doses prior to or soon after extinction (exposure) trials in animals.[25-27] Use of short-term dosing as opposed to long-term dosing of DCS may be critical to its intended effect on NMDA receptor activity.[28-30]

Exposure-based treatments in humans rely on extinction to treat the core fears underlying anxiety disorders, and the efficacy of DCS in animal models led to the recent application of DCS for humans with height phobia (acrophobia). Ressler et al[22] randomized 28 participants with acrophobia to 2 sessions of virtual reality exposure therapy preceded in double-blind fashion by administration of single doses of placebo or DCS (50 or 500 mg) taken 2 to 4 hours prior to each of the sessions. Exposure therapy combined with DCS resulted in significantly larger reductions of acrophobic symptoms at 1 week and 3 months following treatment with no difference in efficacy between the 2 doses as well as no reports of adverse effects. Patients receiving DCS also showed significantly greater decreases in objective measures of anxiety during the virtual exposure and significantly greater improvements compared with placebo on general measures of in vivo acrophobic symptoms that were evident early in treatment, and the improvements were maintained at 3 months. Accordingly, this early success for DCS represents a particularly satisfying achievement for translational research; basic science studies of fear and extinction circuits led to the study of NMDA partial agonists in animal learning paradigms and, ultimately, to the demonstration of similar effects in the clinical study of humans.

The goal of the present study was to evaluate whether DCS would enhance the effects of exposure therapy for SAD, a disorder that both is better studied in clinical trials of pharmacotherapy and psychotherapy and is associated with greater clinical disability than acrophobia. To improve the clinical relevance of our work to the treatment of SAD, we studied a greater number of exposure sessions than used by Ressler et al,[22] conducted treatment at multiple sites, and used both individual and group formats to ensure heterogeneity of therapists and settings as would be encountered in actual clinical practice. Also, given evidence that 50 mg may be a sufficient dose for facilitation of exposure-based treatment,[22] we studied only this dose in the context of a randomized, placebo-controlled trial of outpatients with SAD who were seeking treatment at specialty anxiety clinics. We recruited individuals with significant public speaking anxiety because public speaking is a commonly feared social situation that can be easily and realistically created in a group treatment session. Public speaking is also an ecologically valid exposure situation that is easily modified and individually tailored. Furthermore, it has been shown that treatments that primarily target public speaking anxiety generalize to other social fears and have acute treatment effects on more generalized social anxiety symptoms similar to more comprehensive treatments.[31,32] We hypothesized that patients who received exposure therapy plus DCS would show greater reductions relative to patients who received exposure therapy plus placebo in social fears at the study endpoint and at 1-month follow-up.

## METHODS

### PARTICIPANTS

Participants included 27 patients with a principal *DSM-IV* diagnosis of social phobia who visited the Center for Anxiety and Related Disorders, Boston, Mass (n=15), the anxiety clinic at Massachusetts General Hospital (MGH), Boston (n=7), or the anxiety clinic at Southern Methodist University (SMU), Dallas, Tex (n=5). Participants were enrolled in the study between August 4, 2004, and April 5, 2005, with follow-ups completed on May 10, 2005. All of the therapists followed the same protocol of treatment (S.G.H., *Exposure Therapy for Social Anxiety Disorder*, unpublished treatment manual, 1999) and were trained and supervised by 2 of us (S.G.H. and M.W.O.).

Participants from SMU (n=18) and MGH (n=19) who expressed interest in participating in the study were recruited from the community via advertisements that were posted locally. Patients who appeared eligible based on an initial telephone screen were invited for a diagnostic interview by blind and independent clinicians and to meet with a member of the research team who obtained informed consent for the study. Of the outpatients who contacted MGH and SMU, 15 (10 from MGH and 5 from SMU) met inclusion criteria and initiated treatment. Outpatients from the Center for Anxiety and Related Disorders (n=27) were contacted to participate in the study after a diagnostic interview; 17 expressed interest and signed informed consent, but 10 refused to participate in the study. Of the 32 eligible participants who were randomly assigned in double-blind fashion to treatment with exposure therapy plus DCS or exposure therapy plus matching pill placebo, 5 had to be excluded from analysis for the following reasons: 4 patients withdrew after signing the consent form or after the initial treatment session, and 1 patient was excluded owing to a protocol violation. Twenty-seven patients (12 who received exposure therapy plus DCS and 15 who received exposure therapy plus placebo) completed the 5-session treatment. Twenty-three patients (10 who received exposure therapy plus DCS and 13 who received exposure therapy plus placebo) completed the 1-month follow-up assessment. **Figure 1** shows the progress of patients in the study.

The sample characteristics are presented in **Table 1**. The majority of the sample was male (n=19), single (n=16), white (n=16), and had a college degree (n=21). The mean (SD) age of the sample was 33.70 (10.02) years. Other ethnic origins included Asian (n=4), Hispanic (n=3), African American (n=3), and Asian Indian (n=1). Patients in the group that received exposure therapy plus placebo tended to be older than patients in the group that received exposure therapy plus DCS ($t_{25}$=1.72; $P$=.10). Age was therefore entered as a covariate in subsequent analyses. No other group differences were observed.

Diagnostic interviews revealed that 11 individuals had at least 1 additional *DSM-IV* Axis I diagnosis; of these participants, 9 had an additional anxiety disorder and 4 had an additional mood

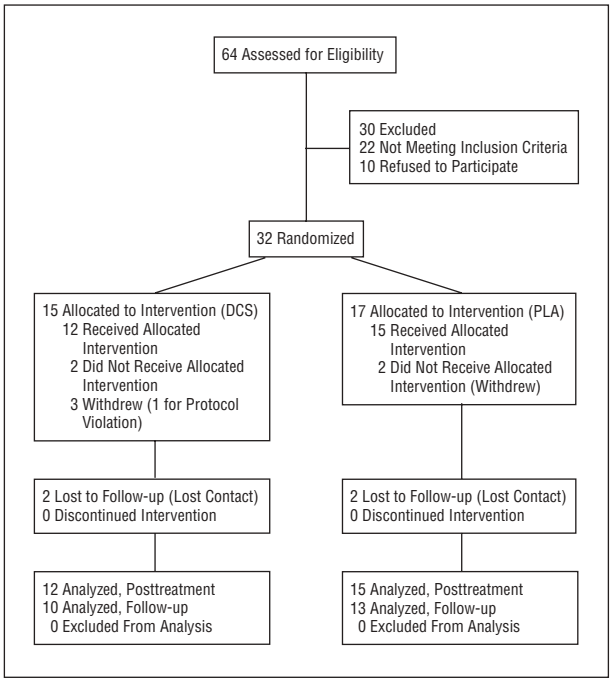


**Figure 1.** Progress of participants in the study. DCS indicates exposure therapy plus D-cycloserine; PLA, exposure therapy plus placebo.

**Table 1. Sample Characteristics**

| Characteristic | Exposure Plus D-Cycloserine* | Exposure Plus Placebo* | *P* Value (2-Sided) |
|---|---|---|---|
| Sample size, No. | 12 | 15 | NA |
| Age, mean (SD), y | 30.08 (7.56) | 36.53 (22.04) | .10† |
| Male | 7 (58.3) | 11 (73.3) | .45‡ |
| White | 8 (66.7) | 8 (53.3) | .70‡ |
| Single | 8 (66.7) | 8 (53.3) | .68‡ |
| College degree | 8 (66.7) | 13 (86.7) | .66‡ |
| Generalized subtype of SAD | 11 (91.6) | 13 (68.7) | >.99‡ |
| Any additional *DSM-IV* Axis I diagnoses | 6 (50.0) | 5 (33.3) | .45‡ |
| Additional mood disorder | 3 (25.0) | 1 (6.7) | .55‡ |
| Additional anxiety disorder | 4 (33.3) | 5 (33.3) | .46‡ |
| Receiving psychotropic medication | 4 (33.3) | 7 (46.7) | .70‡ |

Abbreviations: NA, not applicable; SAD, social anxiety disorder.
*Values are expressed as number (percentage) unless otherwise indicated.
†Value obtained by *t* test.
‡Values obtained by $\chi^2$ test.

disorder. Fewer than half of the patients (n = 11) were receiving a stable dose of psychotropic medications (1 person was receiving a benzodiazepine, 9 were receiving antidepressants, 1 was receiving a β-blocker, and 3 were receiving stimulants). All of the patients receiving psychotropic medication remained stable until 4 weeks after completion of the last treatment session. No group differences were observed.

## STUDY CRITERIA

Inclusion criteria included the following: (1) age of 18 years or older; (2) current *DSM-IV* diagnosis of social phobia that is designated by the patient as the most important source of current distress or interference; and (3) significant fear of public speaking. Diagnostic exclusion criteria included a history of bipolar disorder, psychosis or delusional disorders (as evaluated by the Anxiety Disorders Interview Schedule for *DSM-IV*[33] or Structured Clinical Interview for *DSM-IV*,[34] as explained later), substance abuse or dependence or alcohol abuse or dependence (other than nicotine in the last 3 months), current posttraumatic stress disorder (other comorbid anxiety disorders were allowed as long as they were not the primary source of distress or interference), and presence of psychomotor retardation or suicidality.

Medical exclusion factors included the following: (1) pregnant or lactating women (to determine this exclusion factor, a urine pregnancy test was performed for all of the female participants of childbearing potential prior to administering the study medication); (2) patients with severe unstable medical illness or serious medical illness that required hospitalization; and (3) a history of seizures. Furthermore, only patients who were not receiving psychoactive medication or who were stabilized for at least 8 weeks were eligible to participate in the study.

## MEASURES

Social anxiety disorder and other psychiatric diagnoses were determined by interview with the Anxiety Disorders Interview Schedule for *DSM-IV*[33] at the Center for Anxiety and Related Disorders and by the Structured Clinical Interview for *DSM-IV*[34] at MGH and SMU. Both interviews are well-established, gold-standard structured clinical interviews that contain detailed *DSM-IV*–based diagnostic questions about each anxiety disorder and other diagnostic categories that are important for differential diagnosis (eg, major depressive disorder, dysthymia, mania, alcoholism, substance abuse). These interviews show high interrater reliability for diagnosing social phobia and other diagnoses.[34,35] All of the diagnostic evaluations were conducted by trained and certified clinicians and were reviewed by 3 of us (S.G.H., J.A.J.S., and M.W.O.).

The primary treatment outcome measure was the Social Phobia and Anxiety Inventory (SPAI) score.[36] Additional measures included the Liebowitz Social Anxiety Scale[37] (LSAS) score and the Clinical Global Impression Scale severity subscale[38] (CGI-S) score. The SPAI is a 109-item self-report instrument that has been widely used to assess the cognitive, somatic, and behavioral dimensions of social phobia. This measure is capable of discriminating socially phobic persons from those with other anxiety disorders[36] and from normal controls.[39] Test-retest and internal reliability is high for this scale.[36] Convergent and discriminant validity of this instrument have also been demonstrated.[36,39] The LSAS is a 24-item clinician-administered scale. More recent studies[40] have used this scale as a self-report instrument. The psychometric properties of the self-report scale have been described elsewhere.[40] We administered the self-report version of the LSAS and will report the total score from this instrument. The CGI-S is a commonly used 7-point clinician rating scale to indicate severity. In addition, we also administered the Credibility/Expectancy Questionnaire.[41] The Credibility/Expectancy Questionnaire comprises a total of 6 items; 4 of those items measure expectancy, and 2 items measure credibility of treatment. Patients are asked to rate items on a scale of 1 to 9, with anchors provided for 1 ("not at all logical"), 5 ("somewhat logical"), and 9 ("very logical").

## MEDICATION

D-Cycloserine is approved by the Food and Drug Administration as an antibiotic used in the treatment of tuberculosis in the United States. It is generally dosed at 500 to 1000 mg/d divided twice daily[42] with long-term treatment. The peak blood

levels occur within 3 to 8 hours after dosing, and it is primarily excreted renally with a half-life of 10 hours. No significant adverse effects have been described in any of the recent clinical studies[43-46] examining DCS for cognitive enhancement, even when used in doses of up to 500 mg/d.

### TREATMENT

All of the patients received 5 sessions of individual or group exposure therapy, which is a condensed version of standard exposure therapy that has been found to be efficacious in previous studies.[19,31]

Patients were randomized to either adjunctive DCS or pill placebo administered as a 50-mg pill on each of 4 occasions—1 hour prior to the exposure procedures that compose sessions 2 through 5 of the treatment. The random allocation sequence was generated by numbering containers with the medication. The sequence was generated prior to allocating participants and was concealed until the end of the study. All of the individuals involved in patient care, evaluation, or study supervision were blind to group assignment until the end of the study.

All of the patients were scheduled for sessions 1 week apart. In the first session (60 minutes), patients were provided with a model of social phobia and its treatment with exposure therapy. In sessions 2 through 5 (90 minutes), patients received the blinded study pill, waited 1 hour, and were then introduced to the social exposure procedures. The exposure practices of increasing difficulty consisted of giving speeches about topics chosen by the therapists in front of the other group members or confederates and a video camera. Patients' videotaped performances were then reviewed. At the conclusion of each exposure session, patients were encouraged to continue to apply home-practice strategies (such as giving speeches in front of a mirror). Continued practice of the interventions was considered part of treatment, and patients were asked to refrain from alternative treatment for 4 weeks following completion of the last treatment session.

### ANALYSIS

Data were blindly entered and analyzed with the SPSS version 11.0.1 statistical software package (SPSS Inc, Chicago, Ill). We conducted a 2 (group) × 3 (pretreatment, posttreatment, and follow-up) repeated measure analysis of covariates with the primary measure (total SPAI score) as a dependent variable and age as a covariate to examine changes across all of the 3 assessment points.

In addition, we computed difference scores (ie, pretreatment to posttreatment and pretreatment to follow-up) for each of the treatment outcome measures (SPAI, LSAS, and CGI-S scores). Analyzing difference scores is particularly useful to detect within-subjects changes in small samples.[47] These difference scores were subjected to multivariate analyses of covariance with group (DCS vs placebo) as the between-subjects factor and age of participants as the covariate. Separate analyses were performed for the effects at posttreatment and the effects at follow-up.

Recognizing that a lack of statistical difference may reflect inadequate sample size, we computed controlled effect sizes (Cohen d)[48] by dividing the difference between the mean change of the DCS group and the mean change of the placebo group by the pooled standard deviation.[49]

## RESULTS

### ADVERSE EFFECTS

Administration of the active study drug was characterized by only 2 spontaneous reports of acute adverse effects: vivid nightmares the night after administration of the study drug and the exposure sessions in 1 patient, and euphoric mood and increased energy in an individual with chronic depression (with no symptoms of grandiosity, pressured speech, or reckless behavior).

### PATIENTS' BELIEFS ABOUT GROUP ASSIGNMENT

At 2 of the study sites (Center for Anxiety and Related Disorders and SMU), participants (n = 20) were asked at each session to indicate whether they believed that they were assigned the active medication or the placebo pill. The 2 groups (DCS vs placebo) did not differ in the percentage of patients who believed that they received DCS at session 2 (4% vs 5%, respectively; $\chi^2_1 = 0.00$; $P > .99$), session 3 (5% vs 4%, respectively; $\chi^2_1 = 0.29$; $P = .99$), session 4 (6% vs 7%, respectively; $\chi^2_1 = 0.06$; $P > .99$), and session 5 (5% vs 6%, respectively; $\chi^2_1 = 0.25$; $P > .99$).

### TREATMENT CREDIBILITY

Treatment credibility ratings were completed by all of the participants after the educational session (session 1). Patients' ratings for both treatment expectancy and credibility were moderately high to high and not significantly different between the 2 groups ($t_{25} = 0.57$ and $P = .58$ for treatment expectancy; $t_{25} = 0.60$ and $P = .56$ for treatment credibility). The mean (SD) rating was 6.87 (1.14) for treatment expectancy and 5.70 (1.78) for credibility.

### CHANGES FROM PRETREATMENT TO POSTTREATMENT

The multivariate analyses of covariance with the treatment completers revealed a significant effect of group in favor of DCS (Wilks $\lambda = 0.61$; $F_{3,21} = 4.55$; $P = .01$). The effect of age was not significant (Wilks $\lambda = 0.83$; $F_{3,21} = 1.45$; $P = .25$). Results of the univariate analyses indicated that the effect of group was significant for changes in the SPAI ($F_{1,23} = 9.20$; $P = .006$) and LSAS ($F_{1,23} = 5.73$; $P = .02$) scores. The group effect for changes in the CGI-S scores did not reach statistical significance ($F_{1,23} = 2.60$; $P = .12$). As shown in **Figure 2**, the difference between the DCS and placebo groups increased linearly with time, as illustrated by the SPAI scores. The between-group effect sizes (**Figure 3**) were in the medium to high range.

### CHANGES FROM PRETREATMENT TO FOLLOW-UP

The effects at follow-up mirrored those observed at posttreatment. The between-group effect sizes (**Figure 4**) remained in the medium to high range. The overall multivariate analyses of covariance with treatment completers for pretreatment to follow-up change scores yielded a significant effect for group, favoring DCS (Wilks $\lambda = 0.59$; $F_{3,18} = 4.10$; $P = .02$). The effect of age was not significant (Wilks $\lambda = 0.72$; $F_{3,18} = 2.39$; $P = .10$). Univariate analyses revealed a significant differential group effect on improvements in the SPAI ($F_{1,20} = 12.71$; $P = .002$) and LSAS ($F_{1,20} = 5.70$;

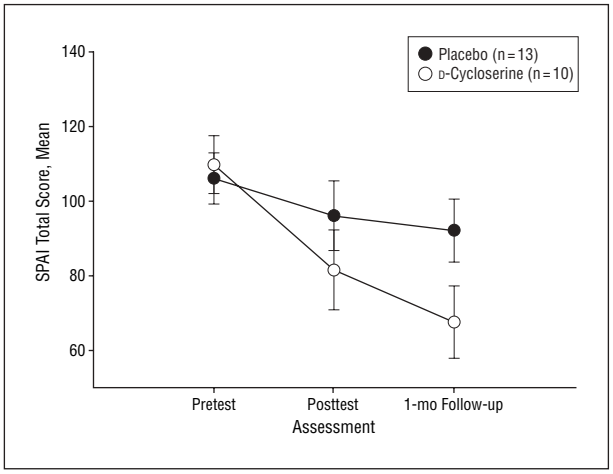


**Figure 2.** Social Phobia and Anxiety Inventory (SPAI) scores at pretest, posttest, and 1-month follow-up assessments of treatment completers. Error bars indicate standard errors.

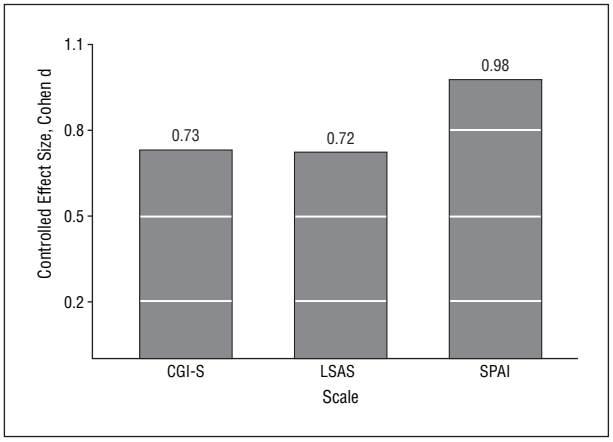


**Figure 3.** Controlled effect sizes (Cohen d) from pretreatment to posttreatment comparing D-cycloserine and placebo (completer analysis). Higher scores favor D-cycloserine over placebo. The cutoffs for small, medium, and large effect sizes are 0.2, 0.5, and 0.8, respectively. CGI-S indicates Clinical Global Impression Scale severity subscale; LSAS, Liebowitz Social Anxiety Scale; and SPAI, Social Phobia and Anxiety Inventory.

$P=.03$) scores. The between-group difference in improvements in the CGI-S scores was not statistically significant ($F_{1,20}=2.69$; $P=.12$). **Table 2** shows the means and standard deviations of the 3 outcome measures (SPAI, LSAS, and CGI-S scores) at pretreatment, posttreatment, and 1-month follow-up in the 2 groups.

## CONCOMITANT MEDICATION USE AND OUTCOME

The use of concomitant medications was not associated with differential pretreatment to posttreatment changes (Wilks $\lambda=0.78$; $F_{3,19}=1.79$; $P=.18$) or pretreatment to follow-up changes (Wilks $\lambda=0.87$; $F_{3,16}=0.80$; $P=.55$). Moreover, concomitant medication use did not significantly affect the magnitude of the differences between the group that received exposure therapy plus DCS and the group that received exposure therapy plus placebo at posttreatment (Wilks $\lambda=0.83$; $F_{3,19}=1.30$; $P=.30$) or at follow-up (Wilks $\lambda=0.95$; $F_{3,16}=0.26$; $P=.85$).

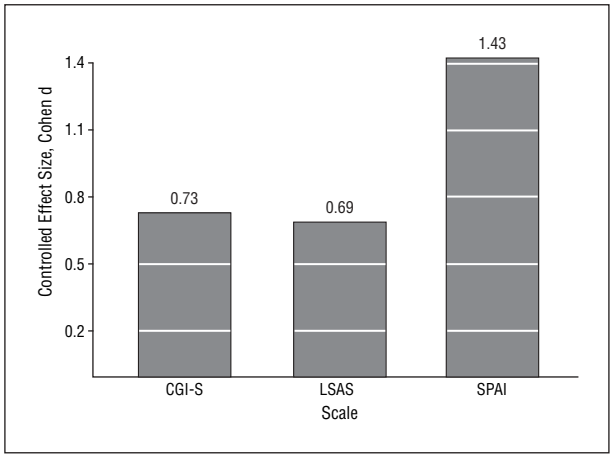


**Figure 4.** Controlled effect sizes (Cohen d) from pretreatment to 1-month follow-up of treatment completers. Higher scores favor D-cycloserine over placebo. The cutoffs for small, medium, and large effect sizes are 0.2, 0.5, and 0.8, respectively. CGI-S indicates Clinical Global Impression Scale severity subscale; LSAS, Liebowitz Social Anxiety Scale; and SPAI, Social Phobia and Anxiety Inventory.

## COMMENT

The results of this double-blind, placebo-controlled pilot study suggest that DCS is a useful strategy to augment the effects of exposure-based CBT for SAD. Patients who received 50 mg of DCS 1 hour prior to exposure therapy that was focused on social performance situations demonstrated significantly greater reductions in general social anxiety symptoms as measured by the SPAI and LSAS scores as compared with patients who received pill placebo before the same exposure intervention. Depending on the measure, the controlled effect sizes (Cohen d; ie, effect sizes of the treatment group compared with the placebo group) ranged from 0.72 (medium) and 0.98 (large) for the treatment changes from pretreatment to posttreatment and between 0.69 (medium) and 1.43 (large) from pretreatment to 1-month follow-up according to Cohen's standards.[48] These controlled effect sizes indicate an advantage of exposure therapy and DCS over standard exposure-based treatment that is already associated with strong treatment effect as delivered in longer treatment protocols.[13,16,17] Moreover, the results indicate that combining DCS with exposure therapy that is focused on a common social performance situation (ie, public speaking) led to a general improvement of social anxiety. This finding is consistent with recent animal studies[50] suggesting that DCS produces generalized extinction of fear. As noted, the NMDA receptor, a glutamate receptor, is known to be critical for multiple forms of learning. For instance, data from studies[51] in a transgenic mouse model overexpressing an active NMDA receptor demonstrated enhanced learning, including both fear conditioning and extinction of tasks. Thus, the effects of DCS as a partial agonist at the NMDA receptor may be responsible for the apparent salutary effect on exposure-based learning. Accordingly, this pilot study provides evidence that DCS may boost an already strong intervention for SAD and facilitate fear extinction. A comparison of our preliminary data with other studies further suggests that combining DCS with a 5-week exposure is

**Table 2. Symptom Severity at Pretest, Posttest, and 1-Month Follow-up***

| Outcome Measure | D-Cycloserine | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Pretest | Posttest | Follow-up | Pretest | Posttest | Follow-up |
| SPAI total score (range, 45-237) | 109.88 (22.46) | 81.74 (27.01) | 67.68 (22.10) | 106.21 (26.05) | 96.21 (37.74) | 92.28 (35.98) |
| LSAS total score (range, 0-100) | 46.76 (15.10) | 30.65 (16.29) | 28.33 (18.28) | 46.57 (20.63) | 36.67 (21.76) | 36.86 (25.03) |
| CGI-S score (range, 1-7) | 4.80 (0.42) | 3.33 (1.23) | 2.80 (1.03) | 4.84 (1.07) | 3.80 (1.15) | 3.46 (1.51) |

Abbreviations: CGI-S, Clinical Global Impression Scale severity subscale; LSAS, Liebowitz Social Anxiety Scale; SPAI, Social Phobia and Anxiety Inventory.
*All values are given as the mean (SD).

at least as effective as standard group CBT. However, it remains to be seen whether DCS also enhances the effects of standard exposure-based interventions or whether it is primarily limited to enhancing the effects of short-term exposure therapy for social phobia.

A large percentage of patients (11 patients [40.7%]) were receiving concomitant medications, which might have confounded the results. However, the use of concomitant medications was not associated with differential treatment changes or group differences at the posttreatment and follow-up assessments. It should also be noted that there are no contraindications to concurrent administration of DCS and psychotropic medications.[42] Because the concomitant use of alcohol and DCS is contraindicated, alcohol intake was prohibited in the study protocol.

Our current findings, the results by Ressler et al,[22] and the results of preclinical animal studies[21] all support a novel use of short-term, intermittent dosing of DCS to aid in extinction learning. The use of individual, weekly doses of DCS rather than long-term dosing may be critical to the effect of DCS on the NMDA receptor[28-30] and may help explain the poor results obtained in long-term dosing paradigms used for other disorders.[52] Furthermore, rather than examining the long-term pharmacologic effects of DCS alone, as has been done in studies of Alzheimer disease[23,24] and schizophrenia,[53,54] our study demonstrated potential efficacy for short-term DCS augmentation to promote therapeutic learning from exposure therapy.

In further support of the benefit of short-term dosing of DCS, most of the extant preclinical data on which the cognitive enhancement effect of DCS is based are from short-term treatment studies[30,55-57] in animals. Direct studies[29,30] of short-term vs long-term treatment with DCS in mice suggest that long-term treatment does not enhance learning whereas short-term treatment clearly does. Thus, the preclinical data show that short-term treatment with DCS is sufficient, and possibly even necessary, to facilitate extinction, obviating the need for long-term administration that could lead to complex compensatory changes at the NMDA receptor. Furthermore, DCS at short-term dosing appears to have negligible adverse effects, as demonstrated by our own study as well. In addition, the relatively low dose of DCS was well tolerated as noted. Although the study by Ressler et al[22] did not find differences in efficacy between the 50-mg and 500-mg doses of DCS, it is possible that as a partial agonist, the use of higher doses may have increased antagonist effects at the NMDA receptor leading to a reduction in efficacy, lending further support to the use of a low-dose strategy.

More broadly, the apparent success of individual dosing of DCS in combination with exposure-based treatment represents a new strategy for combined pharmacologic and behavioral treatment. Rather than combining 2 strategies for anxiolysis, as has been the case of traditional combination treatments for anxiety disorders,[19] the combination of DCS with exposure-based treatments targets the pharmacologic enhancement of therapeutic learning, presumably increasing the salience of safety learning (extinction) achieved through exposure sessions. Whether DCS can also promote other forms of learning (eg, more verbally based psychotherapeutic interventions) remains an open question.

In conclusion, the results of this pilot study provide support for a novel therapeutic strategy—using short-term dosing of DCS as an adjunct to exposure-based psychotherapy aimed at facilitating fear extinction. As with any pilot study, our findings await confirmation in larger studies. The medium to large effect sizes obtained, use of a multicenter design in this pilot study, and apparent independence of study results from concomitant psychotropic use bode well for replication and extension of these findings with larger samples. In addition, we hope that our study will stimulate additional research that directly translates basic science studies of fear extinction and animal learning paradigms into clinical studies for humans in need.

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