ORIGINAL ARTICLE

Cognitive Enhancers as Adjuncts to Psychotherapy

Use of D-Cycloserine in Phobic Individuals to Facilitate Extinction of Fear

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Background: Traditional pharmacological approaches to treating psychiatric disorders focus on correcting presumed biochemical abnormalities. However, some disorders, particularly the anxiety-related disorders exemplified by specific phobia, have an emotional learning component to them that can be facilitated with psychotherapy.

Objective: To determine whether D-cycloserine (DCS), a partial agonist at the *N*-methyl-D-aspartate receptor that has previously been shown to improve extinction of fear in rodents, will also improve extinction of fear in human phobic patients undergoing behavioral exposure therapy.

Design: Randomized, double-blind, placebo-controlled trial examining DCS vs placebo treatment in combination with a precisely controlled exposure paradigm.

Setting: Participants were recruited from the general community to a research clinic.

Participants: Twenty-eight subjects with acrophobia diagnosed by the Structured Clinical Interview for *DSM-IV* were enrolled.

Interventions: After we obtained pretreatment measures of fear, subjects were treated with 2 sessions of behavioral exposure therapy using virtual reality exposure to heights within a virtual glass elevator. Single doses of placebo or DCS were taken prior to each of the 2 sessions of virtual reality exposure therapy. Subjects, therapists, and assessors were blind to the treatment condition. Subjects returned at 1 week and 3 months posttreatment for measures to determine the presence and severity of acrophobia symptoms.

Main Outcome Measures: Included were measures of acrophobia within the virtual environment, measures of acrophobia in the real world, and general measures of overall improvement. An objective measure of fear, electrodermal skin fluctuation, was also included during the virtual exposure to heights. Symptoms were assessed by self-report and by independent assessors at approximately 1 week and 3 months posttreatment.

Results: Exposure therapy combined with DCS resulted in significantly larger reductions of acrophobia symptoms on all main outcome measures. Subjects receiving DCS had significantly more improvement compared with subjects receiving placebo within the virtual environment (1 week after treatment, $P \leq .001$; 3 months later, $P \leq .05$). Subjects receiving DCS also showed significantly greater decreases in posttreatment skin conductance fluctuations during the virtual exposure ($P \leq .05$). Additionally, subjects receiving DCS had significantly greater improvement compared with subjects receiving placebo on general measures of real-world acrophobia symptoms (acrophobia avoidance [$P \leq .02$], acrophobia anxiety [$P \leq .01$], attitudes toward heights [$P \leq .04$], clinical global improvement [$P \leq .01$], and number of self-exposures to real-world heights [$P \leq .01$]); the improvement was evident early in treatment and was maintained at 3 months.

Conclusion: These pilot data provide initial support for the use of acute dosing of DCS as an adjunct to exposure-based psychotherapy to accelerate the associative learning processes that contribute to correcting psychopathology.

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Financial Disclosure: Drs Davis and Ressler have submitted a patent for the use of D-cycloserine for the specific enhancement of learning during psychotherapy. The terms of these arrangements have been reviewed and approved by Emory University, Atlanta, Ga, and Georgia Institute of Technology, Atlanta, in accordance with their conflict of interest policies.

MOST PHARMACOLOGICAL treatments for anxiety and other mental disorders rely on the hypothesis that there are underlying neurochemical or neurophysiological abnormalities that can be corrected with pharmacological treatment.[1] However, there may also be a component to some mental disorders that responds to the emotional learning that occurs with some forms of psychotherapy, such as behavioral exposure therapy.[2] The separate successes of pharmacology and psychotherapy have led to the hope that they can be combined for a more powerful treatment, but to date this hope has not often been realized.[2,3] In some cases, combining these modalities in traditional ways may even decrease the overall efficacy.[4,5]

If the learning hypothesis is correct for some mental disorders, then another way to approach pharmacological treatment is to enhance the learning that occurs in psychotherapy. D-cycloserine (DCS), a par-

tial agonist at the *N*-methyl-D-aspartate (NMDA) glutamatergic receptor,[6,7] has been suggested to be a putative cognitive enhancer based on preclinical[8-10] and limited clinical[11,12] studies. Recent work in our laboratory and others using rodents has demonstrated that acute treatment with DCS enhances the learning process underlying extinction of fear.[13,14] The current study was initiated to determine if similar acute dosing of DCS would enhance learning when combined with a simple form of human psychotherapy, behavioral exposure treatment for specific phobia.

Procedurally, behavioral exposure therapy is very similar to the animal model of extinction of conditioned fear.[15,16] Experimental extinction of fear occurs in both humans and animals when a previously conditioned stimulus is repeatedly presented in the absence of the unconditioned aversive stimulus with which it was initially paired. The neural process of extinction of fear appears to use similar molecular and cellular mechanisms to those involved in fear conditioning.[17] Both fear learning and extinction are blocked by antagonists at the glutamatergic NMDA receptor,[18,19] a receptor known to be critically involved in learning and memory. Furthermore, DCS appears to augment learning in animal models[8-10] and to enhance memory in some human trials.[11,12] We recently found that extinction of conditioned fear in rats was facilitated by DCS given in a 1-time dose prior to extinction training, which consists of exposure to a fearful stimulus in the absence of the aversive stimulus.[13] Importantly, extinction was measured in a subsequent drug-free test of conditioned fear, indicating the facilitation of extinction could not be attributed to an anxiolytic effect of DCS.

We wished to examine the ability of DCS to enhance extinction learning in humans using the most optimally controlled form of psychotherapeutic learning available. Virtual reality exposure (VRE) therapy is ideal for clinical research assessment because exposure and testing are identical between patients, are well controlled by the therapist, and occur within the spatial and temporal confines of the limited therapy environment.[20] This method has proven to be successful for the treatment of specific phobias as well as, more recently, for posttraumatic stress disorder.[20-22] In this study, we directly examined whether acute treatment with DCS would augment extinction of fear during behavioral exposure therapy for patients with acrophobia.

METHODS

PARTICIPANTS

We enrolled 28 volunteer participants recruited from the general community with no currently active psychiatric disorders except for acrophobia by *DSM-III-R*.[23] The diagnosis of acrophobia (subtype of specific phobia) requires an excessive or unreasonable fear of heights that interferes significantly with the person's normal routine and functioning and is characterized by severe anxiety in the presence of height situations. One participant did not return after the preassessment, thus 27 were randomly assigned, via a predetermined and blinded order of treatment assignment, to 3 treatment groups: placebo plus VRE therapy (n=10), 50 mg of DCS plus VRE therapy (n=8), or 500 mg of DCS plus VRE therapy (n=9). Treatment condition was double-blinded, such that the subjects, therapists, and assessors were not aware of the assigned study medication condition. The blind was maintained throughout the study. Twenty-seven participants (11 men, 16 women) completed pretreatment (**Table**), both therapy sessions, and the 3-month follow-up assessment.

Table. Baseline Pretreatment Data of Participant Sample

Characteristic	Placebo (n = 10)	D-Cycloserine (n = 17)	*P* Value
Age, y	44.8 ± 2.3	46.4 ± 2.8	.68
*DSM-IV**	2.1 ± .69	1.6 ± .24	.41
Global Assessment of Functioning	64.7 ± 1.3	65.1 ± .72	.76
Beck Depression Inventory	7.7 ± 4.4	4.2 ± 1.1	.34
State-Trait Anxiety Inventory (state)	34.2 ± 5.6	33.9 ± 2.7	.96
State-Trait Anxiety Inventory (trait)	31.7 ± 4.5	31.4 ± 1.9	.95
Acrophobia Anxiety Questionnaire	65.8 ± 6.2	73.4 ± 5.6	.39
Acrophobia Avoidance Questionnaire	18.7 ± 2.7	24.2 ± 2.5	.17
Attitude Toward Heights Inventory	54.4 ± 1.7	53.9 ± 1.7	.84

Data (age, number of *DSM-IV* diagnoses, and scored values from questionnaires) are presented as mean ± SEM.
*Number of *DSM-IV* diagnoses by the Structured Clinical Interview.

MEASURES

Acrophobia and other psychiatric diagnoses were determined by interview with the Structured Clinical Interview for *DSM-III-R*.[24] Participants were examined with the following battery of screening tests: to examine their fear of heights, the Acrophobia Questionnaire with Avoidance (AAVQ) and Anxiety (AAQ) subscales[25] and the Attitudes Toward Heights Inventory (ATHI)[20,26]; to examine their general levels of depression and anxiety, the Beck Depression Inventory (BDI)[27] and the State-Trait Anxiety Inventory (STAI).[28] Overall global improvement was assessed with the Clinical Global Improvement (CGI-I) scale. During the initial screen, participants also had limited but structured exposure to the virtual reality height environment during a behavioral avoidance test, in which they reported on a 0 to 100 scale (100 being the most intense fear) their subjective units of discomfort (SUDS) for each floor (floors 1-19) of the virtual glass elevator.

Electrodermal skin conductance fluctuations were measured as described previously.[29-31] Finger electrodes (ProComp Module; Thought Technology Ltd, Montreal, Quebec) were worn by the subjects during the initial and posttreatment behavioral assessment tests. Data are reported as the number of skin conductance fluctuations per minute of exposure. Skin conductance fluctuations were measured as in Grillon and Hill,[29] using fluctuation defined as 0.05-µs deviation in baseline skin conductance. Skin conductance fluctuations were averaged over the entire exposure and presented as fluctuations per minute. Each fluctuation was defined as a 2-second or longer deviation of 0.05 µs from the local mean (average baseline ± 30 seconds). Follow-up analyses also examined fluctuations as defined by a 2-second or longer deviation of 5% greater or less than the local mean.

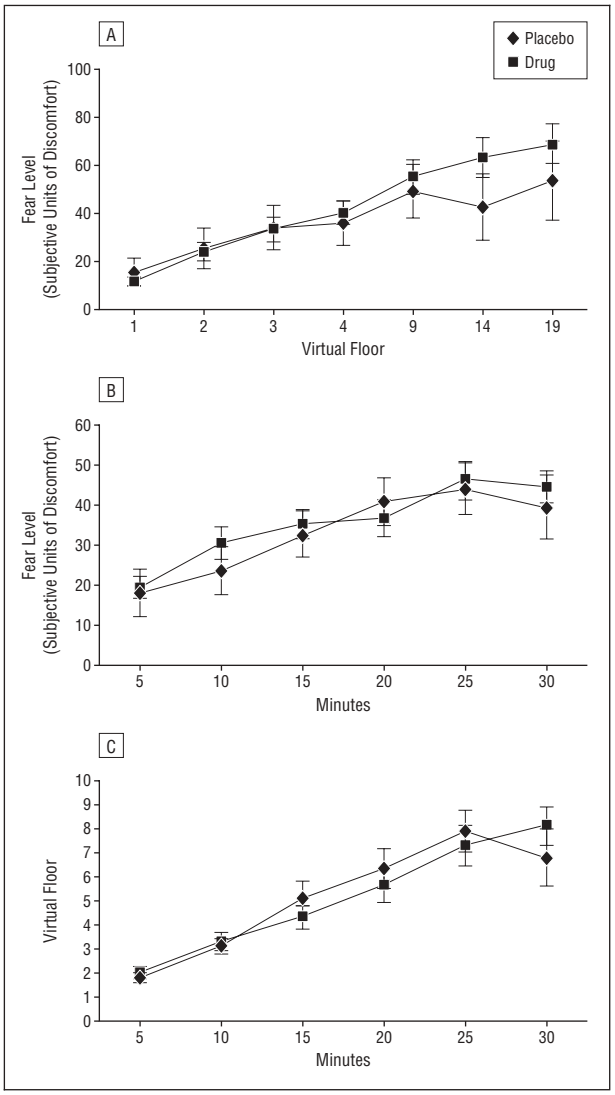

Figure 1. Acrophobia within the virtual environment. A, Level of fear as measured by subjective units of discomfort (1=no fear, 100=maximum fear) during the pretreatment assessment at each successive floor in the virtual glass elevator. B, Subjective units of discomfort during the first treatment session in which subjects were elevated to successive floors at 5-minute intervals. C, Floor to which the subjects were elevated at 5-minute intervals during the first treatment session. There were no significant differences between the groups during the pretreatment subjective units of discomfort measure or either measure during the first treatment session. Error bars indicate SEM.

MEDICATION

D-cycloserine (Seromycin, 250 mg; Eli Lilly and Co, Indianapolis, Ind) was reformulated into 50 mg or 500 mg with identical placebo capsules. These 2 doses of DCS were given acutely prior to psychotherapy for several reasons. The 50-mg dose was based on clinical trials in which 30 to 100 mg per day were effective for implicit memory[12] and subscales of dementia in Alzheimer disease.[32] Furthermore, 50 mg per day appeared to be most effective in the treatment of negative symptoms of schizophrenia.[33] The 500-mg dose was chosen because the efficacy of DCS in the lower dose range (10-250 mg/d) was not effective in several other trials.[34-36] With luteinizing hormone secretion as a measure of NMDA receptor activation, it has also been shown that although 15 to 150 mg did not increase luteinizing hormone, a single dose of 500 mg did but without adverse effects.[37] Thus, single doses as high as 500 mg are likely to be well tolerated and without adverse effects but with clear neuroendocrine effects.[37]

No adverse events occurred during our study. We did not systematically obtain reports of adverse effects although the subjects were routinely asked if they were experiencing any difficulties. Upon breaking the blind, we found no difference between subjects reporting adverse effects with placebo and those reporting adverse effects with DCS. The research protocol used in this study was approved by the Emory University institutional review board, and all subjects gave written informed consent for participation in the study.

TREATMENT

With VRE for fear of heights, we used a virtual glass elevator in which participants stood while wearing a VRE helmet and were able to peer over a virtual railing. Computerized effects gave a real sense of increase in height as the elevator rose. Previous work by our group has shown improvements on all acrophobia outcome measures for treated as compared with untreated groups after 7 weekly, 35- to 45-minute therapy sessions.[20]

Participants underwent two 35- to 45-minute therapy sessions, which is a suboptimal amount of exposure therapy for acrophobia.[20] These 2 therapy sessions were separated by 1 to 2 weeks (average, 12.9 days). Participants were instructed to take a single pill of study medication (placebo, 50 mg of DCS, or 500 mg of DCS) 2 to 4 hours before each therapy session, such that only 2 pills were taken for the entire study. There were no adverse events reported from either group taking placebo or drug prior to exposure therapy.

A midtreatment assessment occurred 1 week after the first treatment (average, 7.2 days), a posttreatment assessment was performed 1 to 2 weeks following the final therapy session (average, 11.5 days), and an additional follow-up assessment was performed 3 months after the therapy (average, 107.5 days).

ANALYSIS

Patients, therapists, and assessors were kept blind to treatment condition throughout the study. All data were entered into the SPSS statistics package (SPSS Inc, Chicago, Ill) by research assistants also blind to condition. Pretreatment variables (Table) were analyzed using *t* tests for independent samples. Posttreatment variables (skin conductance fluctuations, AAQ, AAVQ, ATHI, CGI, and number of self-exposure to heights) were analyzed using 1-way analysis of variance (ANOVA) or repeated-measures ANOVA with time and drug condition as separate factors.

Specific comparisons of different floors and SUDS within treatment sessions were performed with 1-way ANOVA with the between-subjects factor of drug vs placebo group. The effect of interaction between drug group and different floors or drug group and different time points on the SUDS score (**Figure 1**) was performed using multivariate analysis with repeated measures with floor or time as the repeated within-subjects factor and drug condition the independent between-subjects factor. The effect of these interactions on SUDS as the outcome variable for the pre-post analysis (**Figure 2**) was performed with an overall ANOVA with pre-post difference and floor as within-subjects factor and drug group as between-subjects factor.

RESULTS

Twenty-seven participants completed the 2 therapy sessions, with 10 subjects randomly assigned to placebo (5 men, 5 women) and 17 subjects randomly assigned to DCS

(6 men, 11 women). At the pretest assessment, there was no difference in age, number of *DSM-IV*[38] diagnoses, global assessment of functioning, or scores on the BDI, STAI-state, or STAI-trait between placebo and drug groups (Table). There was also no difference in initial acrophobia measures (Table) or in SUDS levels at different floors within the virtual elevator environment (Figure 1A).

Following treatment, we found statistically significant differences between placebo and drug groups for almost all of our primary outcome measures. In the results below, statistics are presented for ANOVA measures with the drug groups both separated and combined. Analysis of our data indicated that there were no significant differences between the 50-mg and 500-mg drug groups for the primary outcome measures of acrophobia (ANOVA, $P>.50$); therefore, the data in the figures are presented with drug groups combined.

D-CYCLOSERINE DOES NOT AFFECT BASELINE LEVEL OF FEAR

Because, based on our preclinical studies, no direct anxiolytic effect of DCS was anticipated, and also because there was no retention interval to allow facilitative effects of DCS on extinction learning, no effects of DCS were anticipated for session 1. Consistent with this, we found no differences between groups in SUDS level during the first therapy session (Figure 1B). During the therapy sessions, participants have some control over how high the elevator is allowed to rise, permitting an analysis of avoidance of heights. During this first session, we also found no differences in the highest floor attained at different time points (Figure 1C). These findings indicate that the presence of DCS during the therapy session did not affect level of fear or avoidance of fear during the therapy.

D-CYCLOSERINE ENHANCES EXTINCTION OF FEAR WITHIN THE VIRTUAL ENVIRONMENT

The results of preclinical studies[13,14] suggest that facilitative effects of DCS might develop during the intersession retention interval and be evident starting at session 2, and we found this to be the case. During the second session, participants in the DCS group experienced lower SUDS than the placebo group (SUDS at 5 minutes, $F_{1,25}=7.1$, $P\leq.01$), and they elevated to higher floors after 20 minutes (mean floor for placebo, 13.0; mean floor for DCS, 15.9; $F_{1,25}=6.3$; $P\leq.01$). This suggests that during the second session there was less fear and avoidance in the group that had received DCS during the first session. This is consistent with the preclinical studies providing evidence of enhanced extinction after only a single session of fear exposure in combination with DCS.[13,14] The DCS group also showed more improvement as measured by participant scores on the CGI scale at the second session (placebo=2.8 vs DCS=2.25, $F_{1,25}=5.2$, $P\leq.05$).

One week after the second session, we performed a posttreatment assessment in the absence of drug and examined the difference scores between posttreatment and pretreatment. The group that received DCS during the therapy sessions showed significantly less fear of heights

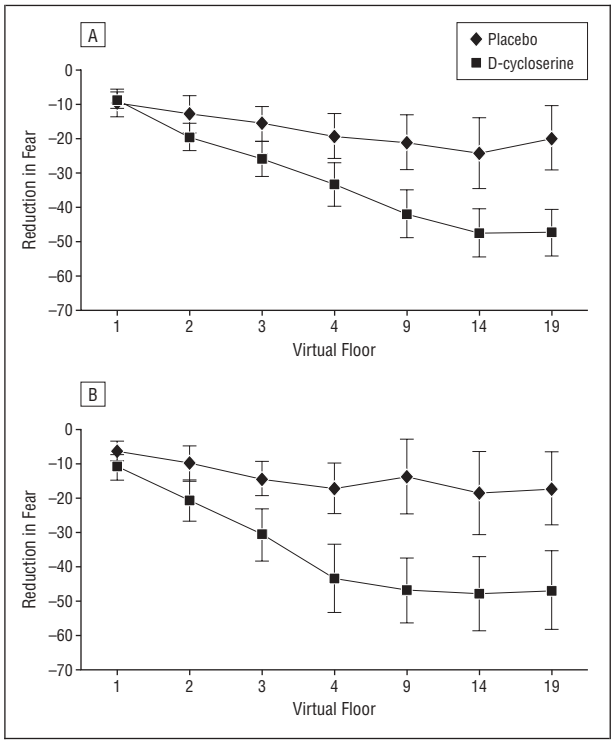

Figure 2. Acrophobia within the virtual environment is improved with D-cycloserine. A, Reduction in fear from pretest to posttest following the 2 therapy sessions measured at the first follow-up assessment. Decrease in subjective units of discomfort level (y-axis) is shown for each floor (1-19) of the virtual glass elevator. Overall analysis of variance was performed using pre-post difference and floor as within-subjects variables and drug group as between-subjects variable. Significant overall pre-post changes were seen: $F_{1,25}=38$, $P\leq.001$. Significant effect of floor was found: $F_{6,150}=89$, $P\leq.001$. Most importantly, significant effect of pre-post × floor × drug interaction was found: $F_{6,150}=3.8$, $P\leq.001$. B, Change in subjective units of discomfort from pretest to posttest at the 3-month long-term follow-up assessment. Statistics were performed as above. Significant overall pre-post changes were seen: $F_{1,17}=21$, $P\leq.001$. Significant effect of floor was found: $F_{6,102}=81$, $P\leq.001$. Most importantly, significant effect of pre-post × floor × drug interaction was found: $F_{6,102}=2.4$, $P\leq.05$. Error bars indicate SEM.

as determined by SUDS at successive elevator floors during the behavioral avoidance test virtual reality assessments (Figure 2A) ($F_{6,150}=3.8$, $P\leq.001$). This difference was also seen if the 2 separate doses of drug were analyzed separately with a repeated-measures ANOVA ($F_{12,144}=2.7$, $P\leq.01$). The continued decrease in fear within the virtual environment in the absence of DCS demonstrates that, as in the animal experiments,[13,14] the enhancement of extinction in humans with DCS is not state-dependent. These data suggest that 2 sessions of VRE therapy in combination with DCS for fear of heights is sufficient for extinction of fear within the virtual environment (Figure 2A).

ENHANCED EXTINCTION WITH D-CYCLOSERINE IS MAINTAINED AT 3 MONTHS

To evaluate how DCS would affect retention of extinction, as well as whether it would generalize to real-life situations outside the virtual reality environment over time, subjects were asked to return for a follow-up session 3 months after their VRE treatment. Twenty-one of the 27 completing participants returned for follow-up as-

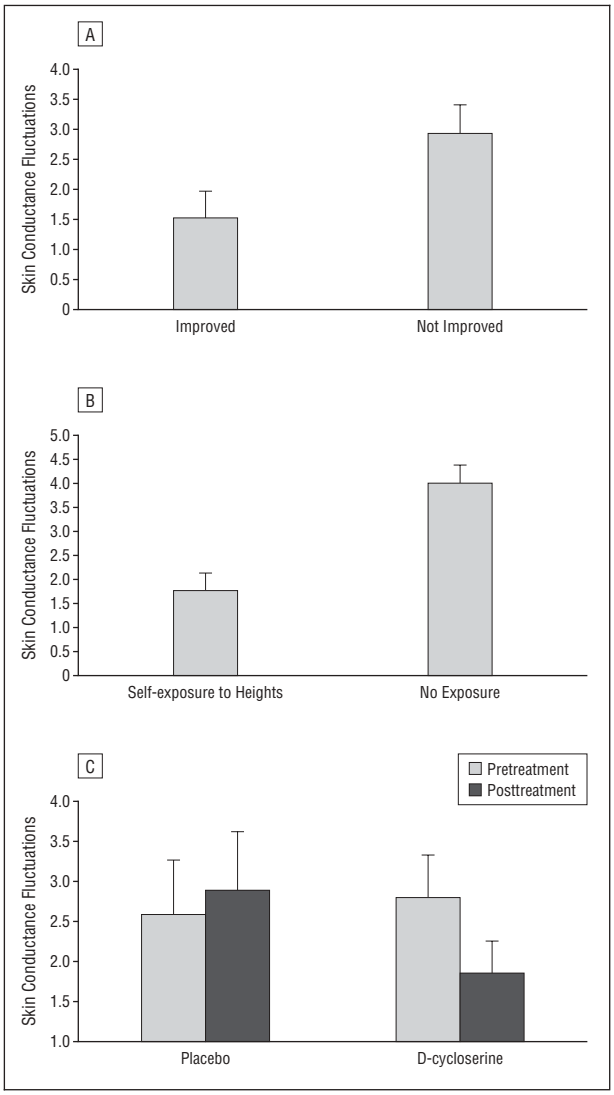

Figure 3. Physiological measures of anxiety within the virtual environment. Spontaneous fluctuations in baseline skin conductance levels are shown as a function of acrophobia treatment response and treatment condition. A, Subjective improvement in acrophobia symptoms. Those reporting improvement in symptoms show significantly lower posttreatment spontaneous fluctuations in the virtual environment ($F_{1,19}$=4.5, P≤.05). B, Decreased avoidance (self-reports of whether they have self-exposed to heights since treatment) also was associated with significantly lower spontaneous fluctuations of skin conductance ($F_{1,19}$=8.26, P≤.01). C, Subjects treated with D-cycloserine during exposure therapy showed significant decreases in posttreatment fluctuations (paired t test, P≤.05) compared with those treated with placebo (P≥.5). Error bars indicate SEM.

sessment (8 placebo [80% of enrolled], 13 DCS [77% of enrolled]). Analysis of the pretreatment data and the 1-week posttreatment assessments showed that there were no significant pretreatment or posttreatment differences on anxiety or fear measures between those who returned for follow-up and the 6 who did not.

At follow-up assessment, subjects were tested again in the absence of DCS for their level of fear in the virtual elevator environment with the behavioral avoidance test. We found that participants who received DCS maintained the specific decrease in fear of the virtual environment across the 3-month period as determined by SUDS during the exposure to virtual heights (Figure 2B) ($F_{6,102}$=2.4, P≤.05). We found no significant differences between the 2 different drug doses. This suggests that the extinction of fear that was enhanced in the drug group during the 2 therapy sessions was relatively robust and lasting.

PHYSIOLOGICAL AROUSAL AND FEARFULNESS DURING VIRTUAL EXPOSURE

The number of spontaneous fluctuations of skin conductance is a common measure of emotional arousal and anxiety, such that those with more fear or anxiety typically show more spontaneous reactivity or fluctuation in their baseline skin conductance during provocation.[29,31] Consistent with this, during the posttreatment behavioral assessment tests, we found that the number of spontaneous fluctuations correlated with the measures of subjective improvement in fear of heights. Those reporting "much" or "very much" improvement at the initial posttreatment assessment test showed significantly fewer spontaneous fluctuations than did those who reported no improvement or worsening (**Figure 3**A) ($F_{1,19}$=4.5; P≤.05; linear regression, r=0.44). Additionally, those who showed less avoidance of heights in the real world since treatment, as indicated by increased likelihood of exposing themselves to real-world heights, also showed fewer spontaneous fluctuations than did those who did not self-expose since treatment (Figure 3B) ($F_{1,19}$=8.26; P≤.01; linear regression, r=0.55).

We also found that those subjects given DCS during exposure therapy had a significant decrease in average spontaneous fluctuations from pretreatment to posttreatment (Figure 3C) (paired t test, P≤.05) compared with those given placebo during the treatment (P≥.50). Subsequent analysis of skin conductance fluctuations using the criterion of a 5% change from baseline in skin conductance instead of an absolute 0.05-µs difference also demonstrated a significant time × treatment effect (repeated-measure ANOVA: $F_{1,19}$=8.0, P≤.01). These data suggest that the improvement in extinction of fear achieved with DCS augmentation during exposure was evident in both subjective and objective physiological measures of fear.

D-CYCLOSERINE AUGMENTS REDUCTION OF GENERAL MEASURES OF ACROPHOBIA

To examine the ability of VRE to heights to reduce symptoms of acrophobia in the real world, we used standard outcome measures of acrophobia that are not specific to the virtual environment. These measures were taken at the pretreatment assessment, the midtreatment assessment between the 2 therapy sessions, 1 to 2 weeks posttreatment, and 3 months posttreatment. These measures were always taken in the absence of medication, and the questionnaires referred to subjects' symptoms of acrophobia in the real world not the virtual environment. **Figure 4** shows the reduction of fear as measured by difference scores between each posttreatment measure and the pretreatment baseline measure for placebo and DCS groups.

For all principal outcome measures, we found significant improvements in the DCS group as compared

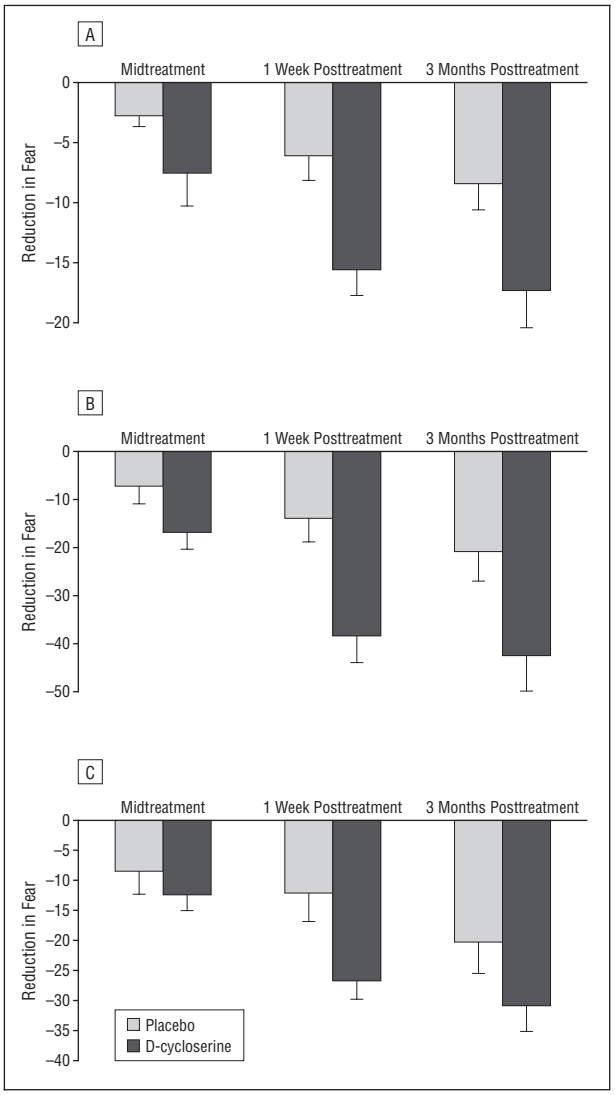

Figure 4. Maintenance and generalization in reduction of acrophobia. Reduction in fear compared with pretreatment baseline on general measures of acrophobia in the real world 1 week after the first therapy session (midtreatment), 1 to 2 weeks after the second therapy session, or at 3-month follow-up. A, Acrophobia Avoidance Questionnaire (repeated-measures analysis of variance, D-cycloserine vs placebo: $F_{1,19}=6.1$, $P<.02$). B, Acrophobia Anxiety Questionnaire (repeated-measures analysis of variance, D-cycloserine vs placebo: $F_{1,19}=7.9$, $P<.01$). C, Attitude Toward Heights Inventory (repeated-measures analysis of variance, D-cycloserine vs placebo: $F_{1,19}=4.9$, $P<.04$). Error bars indicate SEM.

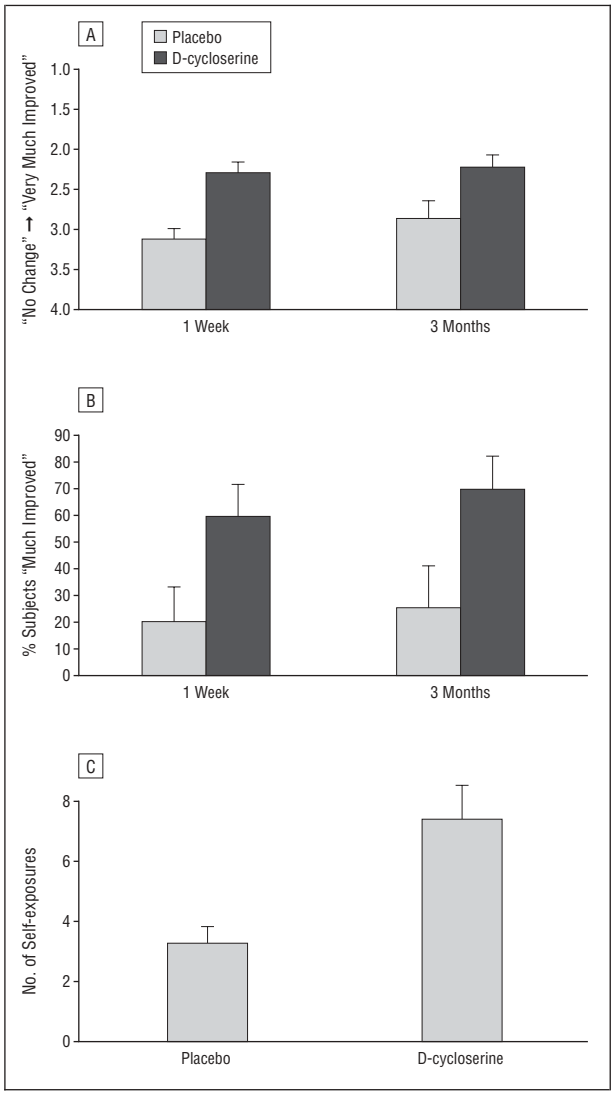

Figure 5. Global improvement and self-exposure. Overall improvement in generalized acrophobia. A, Average Clinical Global Improvement scores (1 = "very much improved," 4 = "no change") for placebo vs D-cycloserine groups at 1 week and 3 months following treatment (repeated-measures analysis of variance, D-cycloserine vs placebo: $F_{1,19}=11.6$, $P\leq.01$). B, Percentage of subjects rating themselves as "very much improved" or "much improved" on the Clinical Global Improvement scale. Subjects receiving D-cycloserine during treatment demonstrated significantly greater subjective improvement compared with those receiving placebo (repeated-measures analysis of variance, D-cycloserine vs placebo demonstrating an overall drug effect but no drug × time interaction: $F_{1,19}=11.5$, $P\leq.01$). C, Reduction in acrophobia as measured by real-world self-exposures to heights during the 3 months following treatment. Subjects receiving D-cycloserine during treatment demonstrated significantly more exposures to heights at 3 months than did subjects receiving placebo ($F_{1,18}=7.7$, $P\leq.01$). Error bars indicate SEM.

with the placebo group in this repeated-measure analysis. This was true for generalized avoidance of heights measures (AAVQ: $F_{1,19}=6.1$, $P\leq.02$), anxiety due to heights (AAQ: $F_{1,19}=7.9$, $P\leq.01$), and general attitudes toward heights (ATHI: $F_{1,19}=4.9$, $P\leq.04$). These significant primary outcomes were also seen when the placebo and the 50-mg and 500-mg drug doses were separated (AAVQ: $F_{2,18}=5.9$, $P\leq.01$; AAQ: $F_{2,18}=4.0$, $P\leq.04$; ATHI: $F_{2,18}=2.5$, $P\leq.10$). These data suggest that the enhanced extinction that occurred during the initial 2 therapy sessions was robust and lasting and also that it was capable of generalization to real-world height situations during the 3 months that followed the therapy.

OVERALL SUBJECTIVE AND FUNCTIONAL IMPROVEMENT ENHANCED WITH D-CYCLOSERINE AUGMENTATION

The final analyses examined general measures of overall improvement in acrophobia as well as evidence of functional gains in the subjects' lives at the 3-month follow-up assessment (**Figure 5**). Average scores on the CGI scale were significantly higher at the 1-week and 3-month follow-up sessions as analyzed with a repeated-

measures ANOVA (Figure 5A) (DCS vs placebo: $F_{1,19}=11.6$, $P\leq.005$). Analysis of placebo, 50 mg, and 500 mg separately also revealed significant differences ($F_{2,18}=5.6$, $P\leq.01$). Furthermore, as seen in Figure 5B, the DCS group showed significantly greater percentages of subjects reporting "much improvement" or "very much improvement" compared with the placebo group at 1 week and 3 months (Figure 5B) (repeated-measures ANOVA: overall drug effect, $F_{1,19}=11.5$, $P\leq.005$, but no drug × time interaction; when analyzed with drug doses separately, $F_{2,18}=5.4$, $P\leq.01$).

A critical measure of functional improvement is the actual number of times the subjects exposed themselves to previously fear-inducing heights in the period following the treatment. Previous studies have demonstrated that subjects successfully treated for acrophobia will expose themselves to heights in the real world following treatment much more frequently than those who are still fearful of heights. When we asked subjects to report the number of significant exposures (eg, peering over a high railing, bridge, etc) that they experienced since the completion of treatment, subjects receiving DCS during treatment reported more than twice as many exposures as those receiving placebo (Figure 5C) (DCS vs placebo: $F_{1,18}=7.7$, $P\leq.01$; when analyzed with drug doses separately, $F_{2,18}=3.6$, $P\leq.05$).

COMMENT

These data demonstrate that DCS facilitates the effects of exposure therapy for the treatment of acrophobia. Participants in the DCS group showed some evidence of enhanced extinction after only a single dose of medication and therapy. Following 2 doses of medication and therapy, they showed significant reductions in levels of fear to the specific exposure environment in both subjective and objective physiological measures of fear. Finally, we found that 3 months following the 2 treatment sessions, the DCS participants showed significant improvements on all general acrophobia measures, their own self-exposures in the real world, and their impression of clinical self-improvement.

Our data indicate that participants receiving DCS experienced no change in anxiety or fear during the exposure paradigm so that the enhancement of extinction is not due simply to altered intensity of exposure. Additionally, the placebo and drug groups were evenly matched on all measures prior to the study (Table), suggesting that pretreatment variables did not contribute to the differential improvement in groups. The slightly higher but nonsignificant depression scores in the placebo group compared with the DCS group (BDI=7.7 vs 4.2) raised the issue of whether subclinical depression could account for some of the differences seen. To test this hypothesis, we reanalyzed all the primary outcomes with pretreatment BDI as a covariate. In all cases (1- or 3-week SUDS, skin conductance fluctuations, AAQ, AAVQ, ATHI, CGI, and self-exposure), none of the covariate analyses were significant ($P=.12$-$.88$). Therefore, the data presented here specifically support the role of DCS during exposure therapy contributing to the resultant enhanced improvement in acrophobia.

It is interesting to note that we did not see an apparent increase in extinction during the treatment session but only between sessions. This finding was expected in part because preclinical studies[13,14] on the effect of DCS on extinction of fear in rats found that extinction seemed to occur during the postacquisition period. Furthermore, it has also been suggested that the NMDA-dependent phase of extinction training occurs during the postextinction consolidation period.[39]

What is the mechanism of this enhancement of behavioral extinction in humans? Although it is possible that DCS somehow specifically enhances extinction, the current literature would suggest that it enhances associative learning in general and thus enhances extinction as a form of learning. The specific evidence that DCS enhances extinction in a learning-specific way again comes from preclinical evidence in rodents. When combined with repeated exposure to the conditioned stimulus, the DCS-treated animals showed accelerated extinction. However, this reduction was not seen when the animals were simply placed back in the fear-conditioning context in the absence of the conditioned stimulus. Thus, DCS did not reduce fear by itself but only facilitated the specific process of extinction of fear in combination with the exposure.[13,14]

Evidence suggests that DCS facilitates other forms of learning in animal models.[8,10,40-42] This is thought to occur through DCS-mediated enhanced activity of the NMDA receptor, a glutamate receptor known to be critical for multiple forms of learning. *N*-methyl-D-aspartate antagonists have been shown to block the formation of fear memories with fear conditioning[43,44] as well as to block the process of extinction of conditioned fear.[18,45] Furthermore, a transgenic mouse that overexpressed the most active NMDA receptor subunit, NR2B, showed enhanced learning and memory on numerous spatial tasks as well as with both fear conditioning and extinction of fear.[46] The data in our study do not directly address whether DCS is augmenting the cognitive component or associative component of learning. However, based on the animal literature on mechanisms of extinction, we believe that the most simple and concise explanation of the data is that DCS primarily enhances the associative component of extinction learning that occurs with exposure therapy.

It is also of interest that we found increased self-exposures in the early and late postassessment periods in the DCS groups compared with the placebo group. We cannot rule out the possibility that DCS treatment during exposure somehow increased the amount of self-exposure in the days and weeks after treatment (off drug) and that those self-exposures accounted for some of the primary outcome findings. However, we believe that even if this were true, it would not detract from the overall finding that only 2 administrations of drug during exposure-based psychotherapy significantly improved reduction of fear compared with the placebo result. Indeed, it would seem to support the idea from the animal literature that the DCS treatment enhanced extinction so that subjects were less fearful in the real world and less likely to avoid heights, providing further evidence for improvement in the DCS-treated subjects.

In some human trials for the treatment of Alzheimer disease, DCS has been shown to be partially effective on subscales of memory improvement.[11,12] However, some studies have failed to find a significant effect on human memory.[35,36,47] We propose that a principal difference between those studies, our current study, and the animal literature is the frequency and chronicity of drug dosing. The previous human studies used chronic daily dosing for weeks to months compared with single dosing in this study and in animals. In fact, Quartermain et al[42] explicitly examined acute vs chronic dosing of DCS in mice for improvement of spatial learning. They found that a single dose of drug enhanced learning whereas 15 days of drug had no effect.[42] Most psychiatric medications have their intended psychotropic effect through chronic mechanisms that often involve receptor, cellular, and systemic regulatory mechanisms that are quite distinct from the acute pharmacological drug effect. Tachyphylaxis, among other regulatory phenomena, is likely to occur with prolonged activation of the NMDA receptor. Desensitization of the NMDA receptor complex has been demonstrated in cell culture with prolonged exposure to DCS and other glycinergic ligands.[48] In contrast to other types of psychotropic medication, DCS may need to be taken on an acute and not chronic dosing schedule to achieve the intended effect of functionally enhancing NMDA receptor activity. This hypothesis remains to be directly tested in an acute vs chronic dosing study in humans.

There are several limitations to this study. First, this is the initial pilot study of the use of DCS to facilitate extinction of fear in humans. As such, the results and interpretations from this study need to be examined in the context of a pilot study and will depend in part on further replication. Because of the relatively small sample size, the study was not adequately powered to demonstrate significant differences between the DCS doses used. Additionally, none of the measures used in this study are without their limitations. All of the psychological measures are by definition subjective, and the physiological measure of skin conductance fluctuation may also be affected by external stimuli and the subjects' movements. As outlined in "Methods" and "Results," we made every attempt to control for these issues and to demonstrate that the physiological and subjective measures of fear were correlated. Finally, there are obvious differences in how routine in vivo exposure therapy for phobias is performed compared with VRE therapy that may impact effectiveness. Future studies examining the ability of DCS to augment exposure therapy for different disorders of fear dysregulation are needed and eagerly anticipated.

The use of a medication that is taken only in conjunction with and for the specific purpose of accelerating learning that occurs in psychotherapy would have important implications. Although specific phobia provides the most easily testable disorder that is amenable to behavioral exposure therapy, this form of therapy is also the mainstay of treatment for other anxiety disorders, such as panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder. In addition, the process of extinction of conditioned cues is thought to be important for recovery from disorders of substance dependence.[49] Finally, it is possible that the therapeutic factor of other forms of psychotherapy relies in part on the process of extinction through imaginal exposure. If such future studies prove successful, the use of cognitive enhancers to specifically potentiate the learning that occurs with psychotherapy could significantly alter the theory and practice of psychiatry. Importantly, it suggests new therapeutic approaches for patients with refractory anxiety disorders that are unresponsive to current treatment options.

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