Dose Timing of D-Cycloserine to Augment Cognitive Behavioral Therapy for Social Anxiety Disorder

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Abstract
The use of d-cycloserine (DCS) as a cognitive enhancer to augment exposure-based cognitive- behavioral therapy (CBT) represents a promising new translational research direction with the goal to accelerate and optimize treatment response for anxiety disorders. Some studies suggest that DCS may not only augment extinction learning but could also facilitate fear memory reconsolidation. Therefore, the effect of DCS may depend on fear levels reported at the end of exposure sessions. This paper presents the rationale and design for an ongoing randomized controlled trial examining the relative efficacy of tailoring DCS administration based on exposure success (i.e. end fear levels) during a 5-session group CBT protocol for social anxiety disorder (n = 156). Specifically, tailored post-session DCS administration will be compared against untailored post-session DCS, untailored pre-session DCS, and pill placebo in terms of reduction in social anxiety symptoms and responder status. In addition, a subset of participants (n = 96) will undergo a fear extinction retention experiment prior to the clinical trial in which they will be randomly assigned to receive either DCS or placebo prior to extinguishing a conditioned fear. The results from this experimental paradigm will clarify the mechanism of the effects of DCS on exposure procedures. This study aims to serve as the first step toward developing an algorithm for the personalized use of DCS during CBT for social anxiety disorder, with the ultimate goal of optimizing treatment outcome for anxiety disorders.

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Introduction

Whereas ample evidence supports the efficacy of cognitive behavioral therapy (CBT) for anxiety disorders, response rates leave considerable room for improvement.[1] Attempts to improve treatment response with combined CBT and anxiolytic pharmacotherapy have led to disappointing results.[2,3] One promising strategy for strengthening the effects of CBT has been the use of pharmacological agents that augment core learning processes in CBT. One important element in CBT for anxiety disorders is exposure procedures, which rely of extinction learning. Preclinical research has shown that extinction learning is blocked by antagonists at the glutametergic N-methyl-D-aspartate (NMDA) receptor, whereas d-cycloserine (DCS), a partial NMDA agonist, augments such learning in animals.[4]

In clinical settings, a number of studies have shown that DCS also appears to augment the effects of exposure therapy.[5] In one of the first human trials, patients with social anxiety disorder (SAD) who received 50 mg of DCS one hour prior to each of five exposure sessions had greater reductions in social anxiety symptoms at post-treatment and one-month follow-up than those who received exposure therapy plus pill placebo.[6] Findings were replicated by Guastella and colleagues.[7] Similarly, promising results were reported in the treatment of height phobia[8] and panic disorder.[9] In contrast, a number of studies have found minimal to no benefits for DCS augmentation of exposure procedures for various clinical and subclinical anxiety problems.[10–14] In the largest DCS trial to date (n = 169),[12] patients with SAD showed a significantly faster rate of symptom improvement than those receiving placebo, but no differences were observed in the response or remission rates at post-treatment and 6-month follow-up. In addition to within-session changes, between session fear reduction also appears to be of importance, as shown in a recent trial with Iraq and Afghanistan veterans.[15] After six sessions of virtual reality exposure therapy, participants showed a greater reduction in PTSD symptoms with d-cycloserine augmentation when extinction learning was well achieved between sessions, which was quantified as the average decrease in peak subjective distress ratings across successive exposure sessions. This effect was not observed when the exposure sessions were combined with alprazolam or placebo.

One possible explanation for these inconsistent findings is related to the extent to which extinction learning has occurred. Consistent with this hypothesis are the results of a re-analysis of the study by Hofmann and colleagues.[12] The results demonstrated that relative to placebo, patients receiving DCS showed greater symptom improvement at each session when self-reported fear levels were low at the end of the prior exposure session.[16] Conversely, patients who received DCS and whose end fear levels were high at the prior session showed less symptom improvement than those taking placebo. At post-treatment, patients receiving DCS whose average fear level at the end of each exposure was low to moderate showed superior outcome to those receiving placebo. Similar results were found in another trial with height phobic patients in which DCS was administered post-session.[17]

It may then be best to selectively administer DCS only after exposures in which end fear levels are low, as DCS can make "good" exposures better and "bad" exposure worse.[18] This is based on findings from animal studies suggesting that NMDA antagonists impair reconsolidation of fear memories, whereas DCS appears to enhance reconsolidation of fear memory.[19] A critical condition determining whether DCS augments extinction learning or reconsolidation appears to be the length of memory reactivation and extinction training sessions. If the extinction session (and the period of stimulus re-exposure) is brief, reconsolidation processes are dominant, whereas extinction processes dominate in longer sessions.[19] Therefore, if fear does not sufficiently decrease during exposure therapy, fear memory reconsolidation may occur and DCS can facilitate this counter-therapeutic process. To test the hypothesis that success of DCS depends on the level of fear experienced at the end of exposure, the present study will examine the effect of selectively administering DCS to patients after exposures in which end fear levels are low.

Methods

Study Design and Objectives

The primary objective of this study is to optimize the application of DCS to augment exposure therapy. We will examine the relative efficacy of tailoring post-session administration of DCS based on end fear levels during a five-session exposure therapy protocol for SAD. Tailored post-session DCS administration will be compared to the most common application of DCS in prior research, which is unselective DCS administration before exposure sessions, as well as unselective post-session DCS administration in order to determine whether post-session DCS administration needs to be tailored. We will also include a placebo condition. We hypothesize that selectively administering DCS when fear levels are low at the end of exposures will lead to greater reductions in social anxiety symptoms at post-treatment and follow-up compared to placebo, unselective pre-session DCS administration, and unselective post-session DCS administration.

A secondary aim is to examine whether DCS enhances fear extinction retention in a laboratory setting. Doing so will allow us to make inferences about the mechanism of action through which DCS enhances outcomes (i.e. whether its effects are due to increased fear extinction retention), and to better interpret any possible null results of the clinical trial (e.g. DCS may work in an experimental paradigm but not in a clinical setting). To examine the effect of DCS on fear extinction retention, a subset of participants will complete a computerized protocol involving a fear conditioning procedure, fear extinction training, and fear extinction retention testing on three separate days, while receiving DCS or pill placebo prior to extinction training. We hypothesize that participants receiving DCS will show greater fear extinction retention in the laboratory experiment than those receiving placebo.

Participants

Our sample will consist of 156 participants for the clinical trial portion of the study, with a subset of 96 participants completing the optional laboratory-based fear extinction paradigm. Recruitment will be split amongst the three study sites: Boston University, University of Texas at Austin, and Rush University Medical Center. Inclusion and exclusion criteria are listed in Table 1.

Table 1

Inclusion Criteria
Primary diagnosis of SAD[a]
LSAS total score $\geq$ 60[b]
Age $\geq$ 18
Medical clearance[c]
Willingness and ability to participate in the informed consent process/study protocol
Exclusion Criteria
Lifetime history of bipolar or psychotic disorders or obsessive-compulsive disorder
An eating disorder, PTSD, or substance abuse or dependence (other than nicotine) in the past 6 months
Organic brain syndrome, mental retardation or other potentially interfering cognitive dysfunction
History of head trauma causing loss of consciousness, seizure or ongoing cognitive impairment
Significant suicidal ideation or suicidal behaviors within 6 months prior to intake
Significant personality dysfunction likely to interfere with study participation (e.g., being overly aggressive or abusive towards the therapists or group members)
Currently pregnant or lactating, or women of childbearing potential who are not using medically accepted forms of contraception
serious medical illness or instability for which hospitalization may be likely within the next year
Concurrent psychotropic medication (e.g., antidepressants, anxiolytics, beta blockers) within the 2 weeks prior to initiation of treatment
Concurrent psychotherapy initiated within 3 months of baseline, or ongoing psychotherapy of any duration directed specifically toward treatment of the SAD
prior non-response to adequately-delivered exposure therapy

[a]Primary diagnosis of SAD as defined by DSM-5 criteria[20]

[b]Liebowitz Social Anxiety Scale (LSAS)[21]

[c]Physical examination and laboratory findings without clinically significant abnormalities

Screening and Randomization

Individuals interested in the study will undergo a psychiatric evaluation to evaluate psychiatric inclusion and exclusion criteria. Participants will be medically cleared by a study physician.

Participants in the optional fear extinction retention experiment will be randomized to receive either DCS or placebo prior to fear extinction procedures. For the clinical trial portion of the study, participants will be randomized to one of four conditions: 1) tailored post-session DCS, 2) unselective pre-session DCS, 3) unselective post-session DCS, or 4) pill placebo. The conditions of the fear extinction experiment will be equally distributed across the four clinical trial conditions such that participants will be equally likely to receive any combination of fear extinction condition and trial condition. Randomization will occur by site using variable-sized permuted block randomization (block sizes varying from 4 to 12). Randomization tables will be created before the first subject is run and sent to the study pharmacist to make the appropriate medication kits. The statistician will check the balance of randomization to control for any unbalanced factors.

Fear Extinction Retention Experiment

The fear extinction retention experiment will occur on three separate days prior to treatment. Participants will undergo conditioning procedures on Day 1, extinction learning on Day 2, and extinction recall and fear renewal on Day 3. Day 1 and Day 3 sessions will take place no more than seven days apart. DCS or placebo will be administered immediately prior to the Day 2 procedures to examine whether DCS enhances extinction recall and reduces fear renewal on Day 3.

Experiment procedures are based on a previously validated fear conditioning and extinction paradigm.[22] During each portion of the experiment, recording electrodes will be attached to the palm of the participant's left hand to measure skin conductance response (SCR), and stimulating electrodes will be connected to two fingers of the participant's right hand to deliver an electric shock. SCR will be measured through a 9-mm (sensor diameter) Sensor Medics Ag/AgCl electrodes. For each trial, participants will view a computer monitor with an image of one of two different rooms containing an unlit lamp for 6 seconds. The lamp will then be "switched on" to one of two colors for 12 seconds, which will serve as the conditioned stimulus (CS). One of the two colors will be paired with an electric shock (the unconditioned stimulus, or US), while the other color will not. The shock will have been previously selected by the participant to be "highly annoying but not painful" and delivered for 500 millisecond through electrodes attached to the second and third finger of the right hand. The inter-trial interval will last an average of 15 seconds. The stimulating electrodes will remain attached to the fingertips throughout the experiment, but the US will be administered only during the Conditioning session on Day 1.

On Day 1, the to-be CS+ and the to-be CS− (four trials of each) will be presented within each room in a counterbalanced manner without presentation of the US (Habituation phase). The Conditioning phase will follow with five CS+ trials that will be immediately followed by the US (100% reinforcement), and five CS− trials (i.e., not followed by shock). All conditioning trials will use the same context (one of the two rooms). On Day 2 (Extinction phase), five CS+ trials and five CS− trials will be presented within the extinction context (the room not used during conditioning) with no US presentation. Day 3 consists of the Extinction Recall phase and the Renewal phase. Extinction Recall is identical to the Extinction phase on day 2, while Renewal is identical to the Conditioning phase except without presentation of the US.

For each trial, SCR will be calculated by taking the difference between the highest skin conductance level (SCL) during each 12-second CS+/CS− presentation and the mean SCL during the 2 seconds immediately preceding that trial. The SCR for the CS− will be subtracted from the SCR for the CS+ to create a differential SCR. Performance during Extinction Training and Recall will be assessed by comparing SCR during CS+ trials on Day 2 and 3 with the maximum SCR during the Conditioning phase. Our main outcome of interest will be Extinction Retention, for which we will calculate an extinction retention index based on the ratio of the mean SCR during the first two trials of the Extinction Recall phase to the largest SCR during the Day 1 Conditioning phase. This ratio will be multiplied by 100 to

yield a percentage of the maximum conditioned response, and this value will be subtracted from 100% to yield the extinction retention index.

Therapy Procedures

Consistent with prior clinical trials,[6,7] we will use a 5-session group CBT protocol emphasizing repeated exposure practice. Each group will consist of 4–6 patients and 2 therapists, who will be PhDs or advanced, trained doctoral students supervised by the PIs. In the first session (60 minutes), patients will be introduced to the cognitive-behavioral model of SAD and provided a rationale for treatment with exposure therapy. Sessions 2–5 (90 minutes each) will consist of increasingly difficult public speaking exposure tasks in which each participant in the group will give an impromptu speech on a topic chosen by the therapist in front of the other group members, confederates and a video camera. Video recordings of each exposure will then be reviewed, and participants will compare pre-exposure predictions about their behavior and appearance during the speech task with their actual performance. Participants will be encouraged to apply home-practice strategies.

Pill Administration

Following prior research demonstrating DCS to augment exposure therapy,[6–9] DCS will be administered in 50 mg doses. Administration of DCS at such a dose has been shown to have a benign side effect profile,[23,24] and increasing the dose to as high as 500 mg has not shown additive effect in enhancing exposure-based treatment.[8] DCS and placebo capsules will be identical in appearance and administered by staff blind to study condition and not involved in the assessment or treatment of participants. Participants in the fear extinction retention experiment will take one study pill (i.e.,50 mg DCS or placebo) immediately before Day 2 of the experiment.

The pharmacist will fill three bottles (with one pill type in each) for each patient for each exposure session according to the schedule in Table 2. Patient, therapist, and staff will be blind to the drug condition (DSC vs. placebo) at pre- exposure; and therapists and patients will be blind to the drug condition at post-exposure. Regardless of study condition, research staff will administer a pill (Pill 1) to each participant one-hour before the exposure session and administer a second pill (Pill 2) immediately after the exposure session. In the tailored administration condition, the selection of Pill 2 will be guided by the end fear level. Specifically, DCS will be administered if the end fear is ≤40 (of 100) on the Subjective Units of Distress Scale (SUDS), whereas placebo will be selected if the end fear is >40. A cutoff of 40 and below was selected based on results of our prior clinical trial, which demonstrated that when end SUDS ratings were below 47, DCS showed an advantage over placebo.[16] Two prior studies using the same 5-session CBT protocol found that mean end SUDS ratings were 49.5 (*SD* = 19.2)[12] and 39.1 (*SD = 17.7*).[25] In the latter study, 85% of patients had at least one end SUDS rating of 40 or below, and 67.5% had at least 2 end SUDS ratings of 40 or below, demonstrating that there is sufficient variability in end fear ratings to justify the examination of tailored and non-tailored post-session DCS administration.

Table 2

Pill administration schedule

Condition	Pre-exposure (1st Pill)	Post-exposure (2nd Pill)	
		If SUDS ≤ 40	*If SUDS > 40*
1. Pre-session DCS	DCS	PBO	PBO
2. Placebo	PBO	PBO	PBO
3. Non-tailored post-session DCS	PBO	DCS	DCS
4. Tailored administration	PBO	DCS	PBO

Note: The Table shows the pill administration schedule. All patients receive 2 pills, one before and one after the exposure session. Depending on experimental condition and SUDS at end of exposure, patients receive one of 4 pill combinations. SUDS: Subjective Units of Distress Scale (rated 1–100); PBO: placebo; DCS: D-cylcoserine (50 mg).

Outcome Measures

The administration of assessments is detailed in Table 3.

Schedule of Assessments

Table 3

Measures	Screening	Baseline	Each Session	Post-treatment	1 mo. Follow-up	3 mo. Follow-up
SCID or ADIS	X					
Medical Screening	X					
Primary Outcomes						
LSAS	X	X	X	X	X	X
SPD-SC Form	X	X	X	X	X	X
Fear Extinction Paradigm (optional)	X[a]					
Secondary Outcomes						
MADRS	X	X	X	X	X	X
Q-LES-Q		X		X	X	X
ASC		X	X	X	X	X
SAFE		X	X	X	X	X
SAQ		X		X	X	X
Exposure Success						
SUDS			X[b]			
Heart Rate			X[b]			
Salivary Cortisol and Alpha Amylase			X[b]			
Moderators and Predictors						
Demographics	X					
NEO-FFI		X				
PSQI		X				
CSD			X[c]			
Audio-recorded speech			X[d]			
CEQ			X[e]			
Adherence			X			

Note: ADIS = Anxiety Disorder Interview Schedule; SCID = Structured Clinical Interview for DSM Disorders; LSAS = Liebowitz Social Anxiety Scale; SPD-SC Form = Social Phobic Disorders Severity and Change Form; ASC = Appraisal of Social Concerns; SAFE = Subtle Avoidance Frequency Examination; SAQ = Social Anxiety Questionnaire for Adults; MADRS = Montgomery Asberg Depression Rating Scale; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; PSQI = Pittsburgh Sleep Quality Index; CSD = Consensus Sleep Diary. SUDS = Subjective Units of Distress Scale; NEO-FFI = NEO Five Factor Inventory of Personality; CEQ = Credibility and Expectancy Questionnaire.

[a] The fear extinction experiment will be scheduled after participants are deemed eligible from the ADIS/SCID and medical examination.

[b] Indicators of exposure success are measured during sessions 2–5 only, and salivary cortisol and alpha amylase samples will be collected at sessions 2 and 5 only.

[c] Subjects will complete the CSD the night before and the night after each session.

[d] Recordings of speeches from session 2 only will be saved for further analysis.

[e] The CEQ will be administered after the first session only.

Data Analysis

We will assess the equivalence of the treatment groups on key baseline variables and any variables that differ among groups will be used as covariates in the final analyses. We will examine missing data patterns, dropout rates, and distributional properties of measures and use transformations to improve distributions if necessary. We will use pattern mixture modeling to assess the effect of missing data.[26] We will rerun our analyses coding for various missing data patterns (no missing data, sporadic

missing, dropouts, etc.) to determine 1) if missingness impacts our findings and 2) how the differences between treatment conditions depends on the missing data pattern.

We will use multilevel modeling (MLM) to evaluate the effect of condition on our continuous outcome measures (LSAS, SPD-SC severity, MADRS, QLES-Q) and generalized linear mixed modeling (GLMM, which is MLM with a logistic linking function) to examine DCS's effect on the dichotomous outcomes ("response" and "remission," explained below). MLM is the recommended method for analyzing longitudinal psychiatric data,[27] easily accommodates missing data, and allows inclusion of all subjects in the analysis even if they drop out. In our MLM analyses, the repeated assessments over time will be nested within individuals, which will be nested within treatment cohort, thereby appropriately accounting for correlated scores within cohorts. We will use a piecewise growth curve model, separately modeling change over time during treatment and follow-up. We will test for quadratic trends and include them if significant. Other non-linear models (e.g., exponential models) will be also be tested, and the model that best fits the data (based on AIC and BIC) will be used. Our "time" variable in these models will be coded as "assessment week" and will reflect the number of weeks since baseline. Using this model, we can test differences between tailored DCS administration and the 3 comparison groups (pre-session DCS, post-session DCS, and placebo) by including 3 dummy coded variables as predictors of the growth curve parameters. Each dummy variable will contrast tailored DCS to each of the other 3 conditions.

Definition of Treatment Response and Remission

Treatment "response" is based on the SPD-SC and is defined by an overall change score of 2 (much improved) or 1 (very much improved) as compared to the pre- treatment assessment. "Remission" is defined as an SPD-SC of 2 or 1 and an LSAS total score of < 30. This LSAS cutoff score is supported by a study of 364 patients that used receiver-operating characteristics in diagnosing SAD,[28] and has generally been adopted as the boundary between remitted and symptomatic patients.[29] It should be noted that the goal of this study is to determine effect size estimates for these gold-standard response and remission outcomes. Detecting differences on these dichotomous outcomes would require a very large sample size, and thus these estimates will be used to evaluate whether a larger- scale trial is warranted.

Outcome Analysis

In order to evaluate whether tailored DCS administration produces superior outcomes to pre-session DCS, post-session DCS, and placebo, we will examine if the dummy variable contrasting tailored DCS to the relevant comparison condition is a significant predictor of the intercept. We will alternately "center" the "assessment week" variable at either posttreatment, 1-mo FU, or 3-mo FU to test for significant differences between conditions at each of these time points.[30]

We will also examine a number of possible moderators of the potential superiority of tailored DCS over the comparison conditions (and, secondarily, of the superiority of pre-and post-DCS administration over PBO). We will use the Fournier approach[31] to identify important moderators. This approach uses an algorithmic method to select significant predictors and moderators within each group of potential moderators (e.g., demographics, clinical and personality characteristics). These selected moderators are then combined in a final analysis, which identifies moderators that are significant over and above the other potential moderators. This approach strikes a balance between testing each moderator separately (which substantially increases Type I error due to the multiple tests) and testing all moderators simultaneously (which may substantially increase the likelihood of Type II error).

Power analysis

This study is not powered to detect small differences between treatment conditions, nor is it powered to detect differences on our dichotomous outcomes. We performed power analyses only for our primary outcomes, which were continuous measures of LSAS and SPD-SC. MLM allows the inclusion of all subjects with at least one data point, regardless of missing data and regardless of whether they drop

out. Thus, we based our power analysis on 156 participants and conservatively assumed that, on average, we will obtain 5 out of the 7 total assessments from each subject. The power analyses were calculated using the program PinT 2.12 (Power in Two Level Models).[32]

For our main outcome analysis, we used our similarly sized DCS trial[12] to estimate the variances and covariances required by PinT, and calculated detectable effect sizes for both LSAS and SPD-SC. PinT indicated we would have a power of .80 to detect an effect size as low as d=.296, between a small (d=.20) and a medium (d=.50) effect size. This translates into a difference of 6.59 points on the LSAS and .42 points on the SPD-SC (at post- treatment, 1-month follow-up, or 3-month follow-up). For the Fournier moderator analysis, we assumed five simultaneous moderators in each group, and included their 15 interactions with the 3 dummy variable contrasts. Moderators were modeled as predictors of both the intercept and slope. Using our prior DCS study to calculate the variances and covariances required by PiNT, we found that, with .80 power, we could detect an effect size of d=.466, slightly smaller than a medium effect size.

Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be created to ensure that the safety of study subjects is protected, and the scientific goals of the study are being met. The DSMB will review any proposed amendments to the study protocol, perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will ensure subject privacy and research data confidentiality.

Collection and Reporting of AEs and SAEs

AE information will be obtained by questioning subjects. All new complaints must be recorded. Pre-existing complaints or symptoms that increased in intensity/frequency after having signed the Informed Consent Form must be recorded. All AEs must be characterized in terms of their start/stop dates, start/stop times, intensity, action taken on Intervention, relationship to Intervention, subject outcome and whether or not the AE led to a Serious Adverse Event (SAE). Clinically relevant changes to the intensity/frequency of a reported AE requires a separate entry on the AE Form.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

All serious events occurring between signing of the Informed Consent Form by the subject and signing of the End of Trial Form by the investigator, except those pre-specified in the protocol, must be reported as soon as practical (within 24 hours of awareness) to the IRB and the DSMB.

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