Research Article

A HIGH-THROUGHPUT CLINICAL ASSAY FOR TESTING DRUG FACILITATION OF EXPOSURE THERAPY

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Objective: *Several studies have demonstrated that D-cycloserine (DCS) facilitates exposure therapy. We developed a standardized test of this facilitation (i.e., a clinical assay), with the goal of testing for facilitation more quickly and inexpensively than a full clinical trial.* **Method:** *We developed a standardized brief exposure in which participants with social anxiety disorder gave a videotaped speech. Participants were randomized to receive a single capsule of 250 mg DCS or a matching placebo prior to preparation for the speech. Distress levels were rated during the speech and again, approximately 1 week later, during a speech in an identical situation. Our primary measure of DCS's exposure-facilitating effect was between-session habituation: whether or not the participants showed less distress during the second speech compared to the first. We also measured levels of subjective anxiety and fear of scrutiny.* **Results:** *Subjects randomized to receive DCS prior to their first speech were more likely to show between-session habituation than those who received placebo. We also found greater reduction of performance-related fear overall in the DCS group.* **Conclusion:** *Our clinical assay was able to detect exposure facilitation effects rapidly and in a highly standardized way, and is estimated to take a fraction of the time and costs of a clinical trial. Given the increasing interest in using medications to enhance learning-based psychotherapy, this high-throughput clinical assay approach may be a favorable method for testing novel mechanisms of action, and clarifying optimal parameters, for therapy facilitation. Depression and Anxiety 30:631–637, 2013.*

Key words: *D-cycloserine; exposure therapy; cognitive behavioral therapy; social anxiety; social anxiety disorder; social phobia; anxiety disorders*

INTRODUCTION

Several studies have demonstrated that the *N*-methyl-D-aspartate (NMDA) receptor agonist D-cycloserine (DCS) facilitates exposure therapy in at least most anxiety disorders.[1–7] In these studies, DCS was typically given shortly before exposure sessions in a standard or abbreviated treatment. Several fundamental questions regarding DCS have not been answered by these trials, including the most useful dose of DCS, the proper timing of dose, and whether coprescribed medications or comorbid conditions interfere with the effects. Such unanswered questions will prevent clinicians from optimally using DCS to benefit patients.

We believe that the unanswered questions about DCS are partially due to the standard paradigm of drug development, which has been called into question because of its heavy emphasis on phase 2 and phase 3 clinical trials, which are lengthy, expensive, and frequently

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fail.[8] In addition to these limitations, clinical trials also rarely clarify the parameters of medications such as dosing, timing, and optimal patient population. As a result, some have argued for a new treatment development paradigm: Called *quick win, fast fail*, this paradigm places more emphasis on early human experimental studies (less labor-intensive than full clinical trials) using biological or behavioral intermediates.[9] The intent in such an approach is to allow agents, or methods of using them, to fail before rather than during an expensive clinical trial. We speculated that such a quick win, fast fail approach could be readily applied to exposure enhancement by conducting brief experimental studies (which we will refer to as *assays*) in persons with anxiety disorders. Such a *high-throughput clinical assay* would be ideal for testing what agents might enhance exposure and under which conditions they are most and least efficacious, prior to moving to full-scale clinical trials.

Our idea of a clinical assay builds directly on many past studies. Several studies of DCS have already used abbreviated forms of treatment.[3,5,7] Our intent was essentially to abbreviate intervention further: one session for a single exposure, and one for assessment only. Such a two-session experiment is also suggested by the behavioral literature, in which two-session tests of exposure augmentation have established several enhancements and limitations of exposure: for example, dropping safety behaviors, adding video feedback, as well as the effects of context on return of fear.[10–14] With the development of pharmacological agents that should acutely enhance learning from exposure, the opportunity presents itself to adapt such behavioral tests for rapid detection of the effects of agents of interest.

In essence, then, the idea of a clinical assay is consistent with previous behavioral research, yet relatively new to pharmaceutical intervention research, even in regard to DCS. Whereas other studies of DCS have generally attempted to provide a full, although sometimes abbreviated treatment for a disorder, we focused on a *single exposure* that would not be expected to be sufficient as a treatment. Notably, because this approach involves a single dose of medication, it also maximizes safety and minimizes risk for participants. We suggest that many questions about DCS (and other agents for exposure facilitation) would be well addressed by the use of a quick win, fast fail approach, such as a clinical assay, followed-up with full scale clinical trials.

The usefulness of such a clinical assay, however, is dependent upon its ability to detect the effects of exposure-enhancing agents. In the case of DCS, it is not completely clear that one should expect enhancement of a single session of exposure. Effects for DCS were found for *two* sessions of exposure in participants with clinically significant fear[6]; yet, no effects were found for DCS in a single session of exposure for participants with subclinical levels of fear.[15] We suspect that the latter result was due to the participant population, but the question remains open. Notably, our clinical assay requires less expense than a study focusing on two sessions of exposure: two visits to the laboratory is easier to manage than three or more.

We therefore set out to design a standardized, easily administered behavioral intervention for anxiety. Our intent was to design an assay that could easily and rapidly accrue participants, yet also focus on a clinically meaningful phenomenon. We focused on social anxiety disorder as one of the more common anxiety disorders,[16] and on speech anxiety in particular because it is the most commonly endorsed fear in individuals with social anxiety disorder [17] as well as an extremely common fear in the general population.[18] Because the effects of DCS have appeared most pronounced in abbreviated courses of treatment, as well as the fact that effects for DCS appear to be strongest early in treatment,[4,19] we designed the behavioral intervention to be brief and substandard as a lone intervention. For example, we did not include any of the cognitive components typically included in contemporary cognitive behavioral treatment for social anxiety disorder.[20,21] Our hypothesis was that our clinical assay would detect the effects of DCS on categorical response to exposure in terms of subjective anxiety (i.e., between session habituation). In addition to categorical response, we also examined *degree* of response as well as to what extent any response generalized to a broader measure of fear of being observed in a social situation (i.e., fear of scrutiny).

MATERIALS AND METHODS

DESIGN

This study was approved by an institutional review board and conducted at the Anxiety and Psychotherapy Laboratory at Washington University in 2011. Participants provided informed consent after receiving a written and oral description of the study. Participants meeting criteria for social anxiety disorder with public speaking fear were randomized to DCS or placebo and received a public speaking exposure in the laboratory. Approximately 1 week later (Range 7 to 24 days; $M = 9.17$) participants returned to the laboratory and repeated the exposure task.

PARTICIPANTS

The sample included 34 participants 18 years of age or older who endorsed public speaking fear and met criteria for social anxiety disorder according to the Mini International Neuropsychiatric Interview[22] plus the established cutoff for social anxiety disorder of 30 or above [23] on the Liebowitz Social Anxiety Scale (LSAS).[23,24] Participants were recruited via flyers, posters, website announcements, advertisement, or from another study that did not involve treatment. Participants were invited to Visit 1 if upon screening they appeared to meet eligibility criteria.

Participants were excluded if there was evidence of history of psychosis, history of bipolar disorder, current substance abuse or dependence, or any other condition that would prevent completion of study tasks (e.g., cognitive impairment). Participants were also excluded if they were pregnant (as per urine test) or breast feeding, or if they showed evidence of seizure disorder, kidney disease, or liver disease.

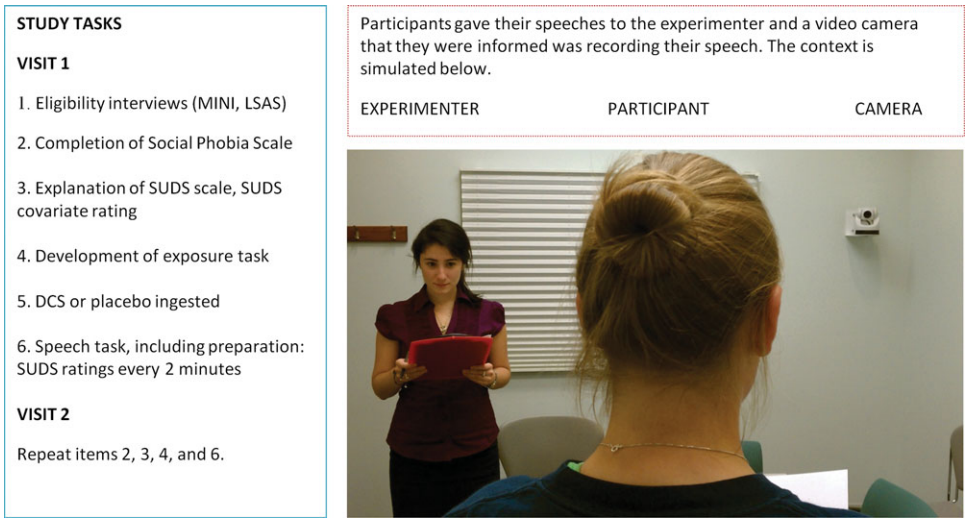

Figure 1. Depiction of sequence of events and measurement across Visit 1: flow chart on left; additional information on right.

RANDOMIZATION AND BLINDING

Participants were randomly assigned to 250 mg of DCS or placebo in identical-appearing capsules by a data manager who had no interaction with participants. Participants ingested their assigned pill immediately prior to beginning preparation for their public speaking exposure. Adequacy of the blind was assessed by having both participants and experimenters guess treatment assignment based on Visit 1 of the study; neither participants nor experimenters were able to discern assignment ($Ps > .15$).

MEASURES AND ASSESSMENTS

Figure 1 depicts the flow of participants through the study, including timing of assessments. The primary outcome measure was of subjective anxiety during the exposures, measured using the Subjective Units of Distress Scale (SUDS), a standard scale in behavioral research[25] that is typically used to estimate degree of between-session change. The SUDS ranges from 0 (no anxiety) to 100 (most anxiety imaginable). The SUDS scale was presented along with anchors based on its use in established treatment.[26] The SUDS was assessed 2 min prior to the speaking task, immediately before the speaking task, every 2 min during the speaking task, and at the end of the speaking task. This scale had excellent internal consistency when several ratings were combined as a scale, which was done here, by averaging the available SUDS ratings for each participant at each time point (Cronbach's $\alpha s > 0.85$ in these data). Subjective anxiety was assessed both in terms of categorical response and overall change. Categorical response was defined as a drop of at least five points in average SUDS across the exposure across visits. Overall change was assessed using the average SUDS across each exposure. SUDS was also assessed prior to the explanation of the exposure, for use as a covariate in analyses of overall change. To test generalization of performance-related fears, we assessed overall fear of scrutiny using the Social Phobia Scale.[27] This 20-item scale assesses severity of fears of being observed or watched in social and performance situations. All measures were conducted at Visit 1 and then repeated in Visit 2; the Social Phobia Scale was repeated after the second speech, in Visit 2.

EXPOSURE INTERVENTION

Participants and the experimenter (a graduate student or well-trained research assistant) worked with participants to develop a tailored exposure designed to lead to clinically significant fear. After explaining the SUDS to the participant and obtaining a current SUDS rating unrelated to the public speaking task, the experimenter developed an appropriate exposure exercise expected to produce a peak SUDS rating of 75. Participants were provided with a rationale that exposure alone is effective for social anxiety (i.e., the exposure should be helpful regardless of medication assignment). Speech exposures were constructed by varying the following flexible elements: topic of speech, availability of notes, time for preparation (2–10 min), length of speech (6–20 min), and reaction of experimenter (supportive, neutral, or unsupportive nonverbal behavior). For example, a participant with only moderately impairing fear of public speaking might require a speech lasting 10 min with 5 min's preparation time and neutral reactions from the experimenter. In contrast, a participant with high fear might only require a 6-min speech with 10 min's preparation time and supportive behavior from the experimenter. Exposure was thus adjusted to produce desired SUDS levels.

It is particularly important to note that the intent of the procedure was to standardize, as precisely as possible, *experience of anxiety*, as measured by SUDS levels, and not to completely standardize superficial procedures (e.g., exact time speaking), which would have had the effect of producing *less* standardization of anxiety response. Ultimately, the modal speech for these participants was 8 min long with 2 min for preparation. Generation and completion of the exposure took less than an hour for all participants.

STATISTICAL ANALYSES

Only those participants completing Visit 2 are analyzed because the intent is to assess the sensitivity of the clinical assay, not evaluate the real-world effectiveness of an intervention package. It is also unclear what the meaning of an intent-to-treat analysis would be when no participants who dropped out provided any ratings after receiving any amount of treatment. Categorical response to DCS was assessed using the χ^2 test. Overall change in subjective anxiety and fear of scrutiny was assessed with a repeated-measures multivariate analysis of covariance (MANCOVA). Time was a within-participant variable, whereas group (DCS versus placebo) was a between-participant variable. Average speech-related SUDS and Social Phobia Scale scores at each visit were entered as dependent variables. The SUDS rating obtained prior to the description of the public speaking task was included as a

covariate because this rating helped control for variance in outcome that was not related to time or group.[28]

RESULTS

SAMPLE CHARACTERISTICS

Participants were assigned to DCS ($N = 18$) or placebo ($N = 16$). Four participants (two DCS, two placebo) did not return for Visit 2 and were not included in any analyses. Two participants became unreachable (change in or loss of phone number: one DCS, one placebo), and two stated that they preferred not to continue in the study (one DCS, one placebo). The remaining participants were mostly women (67%) and had an average age of about 43, with age ranging from 19 to 64. Participants reported ethnicities including white (53%), African American (40%), and Asian American (7%). Most (63%) reported some medication use, with 43% of participants reporting currently using an antidepressant and 23% reporting current benzodiazepine use. Participants were highly socially anxious, reporting an average LSAS score of 79.67 (range: 38–122), where a score of 30 or more is a reliable cut-off for social anxiety disorder and a score of 60 or more is a reliable cut-off for the generalized subtype.[23]

Participants did not differ across group in regard to gender, ethnicity, use of medication, use of antidepressants, LSAS scores at Visit 1, average SUDS for the speech in Visit 1, or Social Phobia Scale ratings at Visit 1 (*P*s > .16). Use of benzodiazepines across groups could not be tested because statistical assumptions were not met (i.e., because too few participant reported use). Groups differed by age ($P = .019$), with the DCS group having an average age of about 49 and the placebo group an average age of 38. This group difference was examined below to test whether it could explain any group effects; it could not.

Participants were asked to report any side effects. One participant, who received placebo, reported that his head had tingled the day of Visit 1. No other participant reported side effects.

RESPONSE RATES AND DEGREE OF CHANGE

Participants in the DCS group were more likely to respond, defined as showing an average SUDS change of at least a 5-point decrease (75%) than those in the placebo group (36%), as assessed by the χ^2 test, $\chi^2(1) = 4.69$, $P = .030$.

As expected, the MANCOVA showed a significant and large multivariate effect for the group by time interaction: Wilk's $\Lambda = 0.78$, $F(2, 26) = 3.70$, $P = .038$, $\eta_p^2 = 0.22$, $d = 1.06$. Figures 2 and 3 depict this interaction effect across the two outcome measures. Participants in the DCS group showed a steeper decrease in scores than those in the placebo group.

The only other variable showing a multivariate effect was time. As also evident in Figs. 2 and 3, scores significantly decreased over time across groups: Wilk's $\Lambda = 0.69$, $F(2, 26) = 5.85$, $P = .008$, $\eta_p^2 = 0.31$, $d = 1.34$. As shown in Fig. 2, in follow-up analyses of covariance (ANCOVAs), it was revealed that the primary source of the group by time interaction was the Social Phobia Scale, for which the interaction had a significant effect ($P = .023$), whereas the effect for average SUDS (Fig. 3) although in the hypothesized direction was not statistically significant ($P = .14$). Further detail is provided in Fig. 4, which displays average SUDS across groups for the five time points that each participant experienced (i.e., values for minutes 6 and 8 are not included in Fig. 4 because many participants ended their speeches at 6 min).

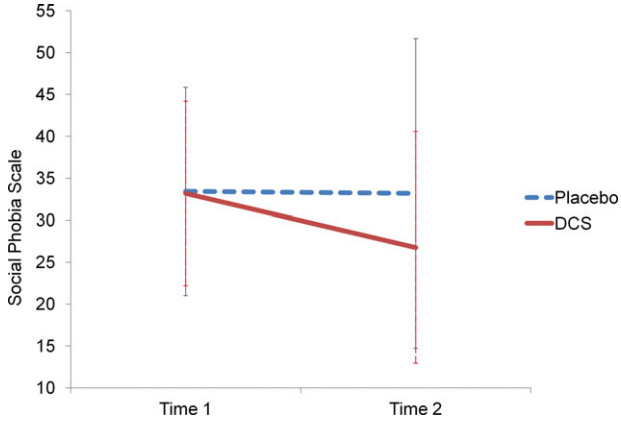

Figure 2. Group (DCS or placebo) by time interaction ($P = .023$) on the social phobia scale: participants in the DCS group show greater change across sessions than participants in placebo group; error bars are standard deviations.

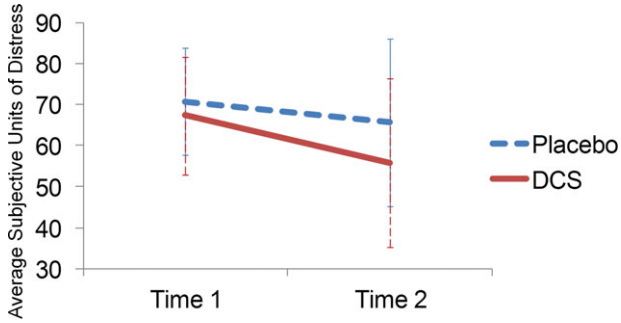

Figure 3. Group (DCS or placebo) by time interaction ($P = .14$) on the Subjective Units of Distress Scale: participants in the DCS group display nonsignificantly greater change across sessions than participants in placebo group; error bars are standard deviations.

The following additional tests were conducted to rule out competing explanations for these effects (data not shown). None of the following additional or alternative analyses altered the large effect seen for DCS by group: including medication or antidepressant use as an additional factor in the analysis; including participant and experimenter guess regarding treatment assignment as covariates; including age as a covariate. A trend ($P = .094$) was observed for a group by time by antidepressant

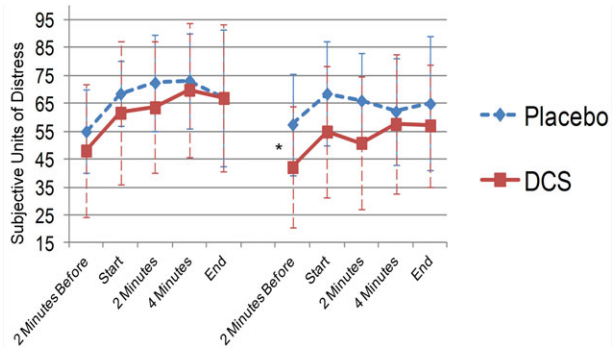

Figure 4. Detailed view of average participant response to each speech in DCS versus placebo: subjective units of distress within speech exposures across sessions for time points experienced by all participants. *$P < .05$; error bars are standard deviations.

interaction, however, on SUDS only, such that average SUDS changed the most for those participants who were both in the DCS group and were not currently taking an antidepressant. Means were in the other direction in the placebo group, such that antidepressant use had no apparent effect.

CONCLUSIONS

We developed a high-throughput clinical assay for testing facilitation of exposure therapy and found that it successfully detected the effects of DCS. The clinical assay we present has several advantages over a full treatment outcome trial, primarily in terms of expense and timing. Due to the reliance on two laboratory visits and only a brief exposure, our clinical assay is faster and much less costly, in comparison to a typical clinical trial. Therefore, our assay fits well with the newer treatment development paradigm of quick-win, fast fail[9] to test DCS and other drug and nondrug candidates for exposure facilitation during phase 1 safety testing or prior to moving to phase 2 and three-type clinical trials. Regarding other candidates, agents with potentially similar pro-neuroplastic or cognitive enhancing properties have been identified,[29,30] but have generally not yet been tested as facilitators of exposure therapy. Many of these agents have FDA approval for another indication or are dietary supplements and can therefore be tested clinically without extensive prior safety testing: the clinical assay might be an efficient means of testing such agents.

It is worth considering whether our current results support the hypothesis that led us to investigate a single-session approach: that DCS should show its strongest effects early in treatment. Guastella and colleagues reported largely moderate effect sizes for DCS versus placebo after five sessions of treatment for social anxiety disorder; the largest effect size was a d of 0.70.[3] Hofmann and colleagues reported moderate-to-large effect sizes after five sessions of treatment for social anxiety disorder, with the largest d being 0.98.[7] In contrast, our obtained multivariate effect of $\eta_p^2 = 0.22$ is equivalent to a d of 1.06. Our obtained effect size is therefore numerically larger than the largest of those seen in studies of abbreviated treatment in the same clinical population. Our observations are thus generally consistent with the hypothesis that the strongest effects for DCS occur early in treatment.

The data presented here provide preliminary support for our clinical assay. We do not wish to overstate the results: additional tests in larger samples are clearly warranted. A test including at least a subsample of participants who complete an entire course of treatment would be ideal, to allow demonstration that early response is a strong predictor of later response, which is an assumption of our approach (and the approach of previous two-session exposure studies). We propose that those tests should also examine the following pressing questions regarding the optimal use of DCS and other prospective agents for facilitating exposure. First, human and animal studies have failed to determine the optimal dose of DCS for exposure augmentation.[4] We propose that finding the minimum required dosage for a robust effect is therefore an important goal, because lower doses could have fewer adverse effects and might delay the onset of the tachyphylactic effect observed with chronic DCS administration.[31]

Second, the ideal timing of medication is unclear from existing trials, although dosage many hours before exposure appears contraindicated, and some studies support the proposition that DCS might be effective if administered *after* exposure.[4] Notably, exposure does not invariably lead to reduced fear. Some evidence indicates that DCS might enhance learning of fear as well as safety, although such an effect has not been clearly demonstrated in humans.[32,33] Giving DCS in conjunction with failed exposures might therefore enhance the effects of that failure. If DCS can be given effectively after exposures have occurred, the administering clinician would have the ability to selectively reinforce only the most effective exposure sessions. Our administration of DCS immediately before exposure is unusual in the human literature: most trials in humans have focused on administering DCS hours before exposure.[4] The fact that we found an effect for DCS when given immediately before the exposure is consistent with the animal literature, in which DCS has routinely been given after exposure and shown effects.[4] Our results therefore suggest, preliminarily, that providing DCS after exposure is likely to be effective, but this proposition requires formal testing.

A third priority is determining whether the effects of DCS might be impaired by common medications or conditions. For example, evidence in rats suggests that dosage with antidepressants may reduce the effects of DCS,[31] although, again, results in humans are thus far lacking. Our data were consistent with that observation, although that result clearly requires replication.

In theory, all of the above questions could be answered in clinical trials. Further, although our clinical

assay might require somewhat fewer participants than a clinical trial (primarily because fewer visits means less attrition), any clinical test of multiple moderators requires thousands of participants to be adequately powered. The point is that answering the above questions, which all involve moderators of treatment effects, would be infeasible with full-scale clinical trials due to cost and time.[34] Yet, these questions also cannot be answered with preclinical models such as fear extinction in animals, given the dissimilarities between this preclinical model and exposure therapy response.[29] The field is thus presented with a stark divide between the promise of agents such as DCS and the ability to use them precisely in the real world. The clinical assay we present represents a potential bridge over that divide and provides answers over a much shorter time. Thus, the clinical assay can complement preclinical studies and clinical trials in clarifying the parameters of DCS in an efficient but clinically meaningful and precise way.

In summary, we demonstrated that our clinical assay design could detect DCS facilitation of exposure therapy. The assay takes a small fraction of the time and costs of a clinical trial. We view such an assay as an excellent complement to clinical trials both in early testing of compounds and in clarifying optimal parameters for their use. Further study is needed to confirm our findings, but our conclusion is that the clinical assay has potential.

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