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The effect of D-cycloserine on social anxiety treatment using a behavioral outcome measure and a post-session administration strategy

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Abstract

Background—The drug D-Cycloserine (DCS) has been used as an adjunct to increase the pace of symptom reductions during exposure therapy for anxiety disorders. This procedure has met with mixed results and many questions remain. Aims: The findings from two investigations are reported here, highlighting important domains for furthering our understanding of DCS effects.

Method—Study 1 ($n = 16$) treated social anxiety among a sample of emerging adults, and in addition to self-report utilized a behavioral measure of symptom improvement to evaluate outcomes. Study 2 ($n = 16$), utilizing a similar design, introduced an algorithm based post-session administration strategy following sessions where anxiety reductions were evident. Both investigations were double-blind, placebo controlled, randomized trials with participants diagnosed with social anxiety. Treatment was an exposure-based CBT-protocol adopted in other investigations that tested DCS.

Results—Findings of Study 1 yielded an interaction effect in favor of DCS for self-reported distress ratings ($p=.02$) and on a behavioral measure of anxiety ($p=.01$). Findings from Study 2 revealed a significant effect for self-reported subjective distress ratings ($p=.002$).

Conclusions—Although limitations of small sample size constrain generalization and limit power, results illustrate some beneficial effects of DCS within the context of exposure-based intervention for social anxiety, yet are discussed in the context of statistical vs. clinical significance and the DCS literature as a whole. Present findings highlight the potential usefulness of a post-session administration strategy and the behavioral measure for future efforts with an eye towards preventing bias through more nuanced and powered studies.

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Keywords

social anxiety; d-cycloserine; exposure therapy; combined treatment

Introduction

A developing area of translational research has investigated the usefulness of the pharmaceutical agent d-cycloserine (DCS) to enhance therapeutic learning. DCS, a partial agonist at the NMDA receptor site of the glutamate system, has been used as an adjunct to exposure-based cognitive behavioral therapy for anxiety disorders and is believed accelerate the therapeutic process (Sheerin, Seim, & Spates, 2014). In human clinical populations, DCS has been examined across a broad range of anxiety disorders. While meta-analyses and systematic reviews support some evidence of DCS enhancement, these effects have generally been small in clinical populations (Bontempo, Panza, & Bloch, 2012; McGuire, Lewin, & Storch, 2014; Norberg, Krystal, & Tolin, 2008; Rodrigues et al., 2014) and findings are often mixed.

A recent Cochrane review (Ori et al., 2015) concluded that although DCS augmentation of CBT has been found to be efficacious in select individual studies, the combined effect size indicates no difference of DCS over placebo augmentation in terms of efficacy, response, or remission in adults generally, or within subgroups of disorders. The review noted, however, that despite no evidence of an effect of DCS, there was also no evidence against its use, suggesting that there is not sufficient evidence to draw conclusions on its use given the present state of the literature.

As noted in the Cochrane review, beyond overall efficacy, more recent studies have provided important information related to administration strategies, moderators of effect, and acceleration of gains as opposed to overall gains, which remain areas in need of further study. Studies have shown that DCS benefits may be specific to accelerated early symptom reduction (Chasson et al., 2010), particularly related to more severe symptoms (Hofmann et al., 2015, Siegmund et al., 2011), or those who required all sessions (de Kleine, Hendricks, Kusters, Broekman, & Van Minnen, 2012) and evident in physiological markers in the absence of self-report changes (Rothbaum et al., 2014). Evidence of DCS effects for specific subsets of patients has further developed to include person-level variables such as personality traits (de Kleine et al., 2014; Smits, Hofmann et al., 2013). Additionally, research has suggested that the amount of within-session learning may moderate the effects of DCS with individuals that demonstrate greater learning exhibiting larger effects (Litz et al., 2012; Smits et al., 2013a; Smits et al., 2013b; Tart, Handelsman, & DeBoer, 2013). This work has highlighted the need for more nuanced investigations to better understand DCS augmentation (McGuire et al., 2014). While examination of differences in speed of recovery remains an important area of focus to meet this need (Ori et al., 2015), studies that focus on behavioral measures and examine moderators are also in need of experimental attention to inform clinical utility. Our group conducted two independent studies examining these two specific domains with relation to DCS augmentation.

The examination of DCS effects via biological and behavioral measures will be important for informing potential enhancement. While the first DCS trial in clinical populations assessed skin conductance (Ressler et al., 2004) the remaining clinical studies cited above have relied solely upon self-report measures. However, Rothbaum and colleagues (2014) recently assessed biomarkers of cortisol and exaggerated startle in addition to self-report and rater assessed symptom measures. These results suggest that biomarkers evidenced significant change with treatment response favoring DCS and highlight the importance of measuring markers of change above and beyond clinical self-report. Overt behavioral indices of change may also prove to be a useful domain of assessment. While anxious behaviors (e.g., fidgeting, avoidance of eye contact) are hallmarks of social anxiety disorder, and are important treatment targets, these behaviors have not been measured in DCS studies to date. In addition to assessing outcomes, an overt measure may be useful in determining exposure success. For example, it is possible someone receiving DCS treatment may demonstrate observable behavioral change (e.g., less shaking, greater approach behavior) separate from and prior to experiencing and reporting a subjective reduction in anxiety or vice versa. As such, Study 1 reported here aimed to investigate overt behavioral changes in anxiety using an observer-rated measure in addition to self-reported anxiety. Furthermore, the dependent variables were assessed at each session to better model change over time as opposed to only end-state outcome. We hypothesized that evidence of DCS improvement across sessions would be reflected in earlier reductions in self-report and behavioral measures of anxiety than for those not receiving DCS augmentation.

The second study investigated the utility of a post-session DCS administration protocol. The importance of refining treatment guidelines to ensure fear extinction is enhanced during treatment has been noted (e.g., McGuire et al., 2014; Smits et al., 2013b). This is based on a growing body of research that has demonstrated DCS enhances treatment outcomes in certain contexts, but when extinction-based learning is incomplete, DCS may have iatrogenic effects; a clear safety issue in the clinical context. A pressing empirical issue in DCS treatment research is the development of an optimal administration strategy. Such a strategy should be based on an explicit identification of extinction learning, whether in the form of changes seen in-session or between-session. This suggestion is based on emerging literature examining the adequacy of extinction learning as an important moderator (Litz et al., 2012; Rothbaum et al., 2014; Smits et al., 2013a; Smits et al., 2013b). Smits and colleagues (Smits et al., 2013a) reported data comparing end of session fear versus within session extinction (determined by end of exposure SUDS ratings and changes from peak to end fear ratings) and found that level of end fear, but not change in fear, was a useful predictor. These findings may provide context for understanding the mixed results with respect to the efficacy of pre-session administration (Smits et al., 2013b). Recent work has also found an association between extinction learning and post-treatment symptom scores for the DCS condition only, with DCS enhancing posttreatment outcomes in those with greater between session learning (Rothbaum et al., 2014). Despite a growing body of research in this area, the optimal method for determining if a session-based exposure trial of DCS is successful has not yet been firmly established (Smits et al., 2013a). The relevance of within session learning (via change in fear levels or end of session fear levels) and between-session learning will be an important research consideration moving forward. The goal of

Study 2 was to examine the utility of post-session administration of DCS, piloting an administration model contingent on in-session evidence of successful exposure trials, as assessed by an algorithm-guided reduction in Subjective Units of Distress (SUDS). A “successful” exposure trial was determined based on a 20% decrease in SUDS during the exposure trial and is further detailed in the study protocol below. Both pilot studies consisted of small-sample illustrative experiments using a randomized double-blind placebo controlled methodology. Both studies used a sample of individuals with social anxiety given the larger body of positive evidence of DCS with this population (e.g., Guastella et al., 2008; Hofmann et al., 2006; Hofmann et al., 2013).

Methods

Human Subjects Approval

Both experiments were approved by the Human Subjects Boards at the university where the study was conducted and a local hospital IRB. Before the medication or placebo was prescribed, all participants met with the study physician for a medical screening to rule out potential contraindications of the medication or placebo. Female participants were also required to take a pregnancy test prior to randomization.

Participants

Participants were recruited from a Midwestern university campus community, although non-students were also eligible for enrollment. For both experiments, following informed consent, participants were interviewed by a trained graduate-level independent assessor with the Anxiety Disorders Inventory Schedule (ADIS; Brown, DiNardo, & Barlow, 1981) in order to determine if they met criteria for social anxiety disorder (SAD) per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). Study 2 (N = 16) required a minimum score of 55 points on the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) indicating moderate social anxiety symptoms. Following the clinical assessment, a medical screening was conducted. Exclusion criteria included: 1) current major depressive episode, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, bipolar disorder or psychosis, 2) DCS-contraindicated current medications or medical conditions (e.g., epilepsy), 3) pregnancy and 4) current use of illicit substances or daily alcohol consumption.

Medication

DCS was purchased under the brand name Seromycin as a 250 mg pill (from the Eli Lilly Company). This dose was used in the current study in order to maintain the integrity of the medication (e.g. no need for pill breakage) and ensure accurate dosage. Parametric studies of dosing magnitude (between 50 mg to 500 mg) have not revealed differential effects (Bontempo et al., 2012). DCS has a half-life of approximately 10 hours and reaches peak blood levels within 2-8 hours when administered orally (Hardman & Limbird, 2001). Participants were randomly assigned to receive DCS or a placebo pill. The placebo pill was compounded by a university-based licensed pharmacist and contained lactose with the same outer seal as the DCS pill. Participants, research assistants, and therapists were blind to intervention condition. However, the psychiatrist and pharmacy staff retained a master list

that identified DCS and placebo assignment. Therapist blindness to participant condition was informally confirmed. Blindness on the part of participants was not formally assessed.

Adverse effects

Prior to each treatment session, participants completed a checklist to indicate potential side effects experienced, any recent changes to medication, and any recent alcohol or illicit substance consumption. The physician checked for any new medications taken prior to administration of the DCS or placebo pill, to ensure no contraindications existed. No significant adverse effects were noted throughout either study. Only two participants indicated mild symptoms. One DCS participant noted dizziness following medication administration at session 2 and one placebo participant reported fatigue at the final session. In line with prior DCS treatment studies, these observations suggest that DCS is generally well tolerated by participants.

Treatment Fidelity

For both studies, treatment fidelity was assessed for 25% of randomly chosen sessions. Videotapes were made (therapists were unaware of which sessions were taped) and two trained raters completed session-specific checklists.

Analytic Plan

Outcome measures for both studies were analyzed using an intent-to treat sample (N = 13 for Study 1; N = 16 for Study 2) using SPSS v. 20 (Armonk, NY: IBM Corp., 2010). A linear mixed effects model, chosen because of its utility with repeated measures and missing data (West, 2009), assessed all serially measured session time points and was used to assess model-based estimates and effect sizes (Cohen's d) calculated across sessions. The best fit for model and covariance structure was determined using the -2 log likelihood (-2LL), using the smaller is better criterion. The maximum likelihood method was used for model estimation. Effect sizes were also calculated and reported given the statistical limitations of small sample size.

Study 1

Measures

Subjective Units of Distress (SUDS)—Immediately following each treatment session, a behavioral avoidance task (BAT) was conducted in which participants were requested to perform an impromptu speech in front of an “audience” of research assistants. Topics were standardized across participants. Anxiety during the BAT was determined via SUDS ratings, from 0 (no distress whatsoever) to 10 (highest distress possible). SUDS scores were recorded at the beginning, middle, and end of each BAT; ratings were averaged to determine a single score per speech, and used as the outcome measure.

Timed Behavior Checklist (TBCL; Paul, 1966)—The TBCL was used as a behavioral measure of anxiety; it is an instrument that lists 20 observable manifestations of anxiety including behaviors such as swaying and extraneous hand movement. These behaviors were scored based on presence or absence throughout 30-second intervals during the BAT by two

trained research assistants, blind to treatment group. A total summary score was derived by summing the number of occurrences at each 30-second interval across the first two minutes of the speech, given variable stop times. Research assistants independently scored the TBCL and compared; points of divergence in scoring were then reviewed again and final determinations were made jointly. TBCL scores in the study ranged from 0-16 across participants and groups.

Session Protocol

The treatment sessions were conducted by a doctoral graduate student trained in exposure-based CBT. The five-session protocol was adapted from a group-based protocol used in a previously published DCS study with SAD (Hofmann et al., 2006). The first session was psycho-educational in nature, with a description of the model of therapy, the nature of anxiety and avoidance, and the process of exposure. Formal speech exposure trials began during the 2nd session, and continued until the final session. Sessions consisted of: in-session in vivo exposures utilizing a public speaking task, feedback, discussion and reaction to exercises with reference to the therapy model, weekly monitoring and discussion of self-exposure practices, discussion of obstacles, cognitive restructuring where relevant, and planning for out-of-session practices.

Results, Study 1

Participant characteristics are presented in Table 1. A total of 16 participants qualified for the study based on the screening session. Fourteen entered treatment and were randomized into the study, with seven participants in each group, and represent the ITT sample. There were no significant differences between groups on age ($p = .07$) or gender ($p = 1.00$). There were no significant differences at the first assessment of the TBCL ($p = .99$), but the DCS group exhibited higher reported SUDS scores ($p = .023$). Thus, session 1 SUDS scores were controlled for in subsequent statistical analyses. Graphs for each outcome measure are presented in Figure 1, and means and standard deviations are available in Supplemental Table 1. Individual participant data for both SUDS and TBCL scores are presented in Supplemental Figure 1 given the wide variability in scores that may be masked with group means. All participants who entered treatment completed at least 4 of 5 sessions, except for one participant in the DCS group who dropped out following session one, prior to initiation of the exposure component. Results for this participant are not included in the ITT analyses.

In addition to main effects of time for both the TBCL and SUDS measures, there was an interaction effect such that the placebo group showed an increase in TBCL scores over time (DCS vs. placebo $F_{1,20} = 7.75$, $p = .01$, $d = 1.24$, 95% CI = .35-2.73). When controlling for SUDS ratings at session one, a significant interaction effect was found ($F_{1,15} = 6.48$, $p = .02$, $d = 1.30$, 95% CI = .20-2.60) indicating greater change in SUDS scores for DCS participants over the course of sessions. The pattern of change in the DCS group for the TBCL was similar to that seen in the SUDS scores, suggesting some correspondence in these measures.

Regarding assessment of treatment fidelity, inter-rater reliability was 98% and adherence to protocol components ranged from 90-100%, with the primary deviation being a lack of therapist modeling, considered an important, but not required component.

Discussion, Study 1

The results of Study 1 provide some support of DCS facilitation during exposure therapy for SAD. The participants in the DCS group evidenced a greater change in TBCL scores and SUDS ratings over time than the participants in the placebo group. However, these differences appear to be more apparent from a statistical standpoint as opposed to a clinical one, particularly given variability between participants in both groups. The TBCL results suggest an objective behavioral measure may provide a useful indicator of treatment response during exposure therapy. The consistent decline in TBCL scores over time for the DCS group suggests that a behavioral measure may capture important clinical change and serve as a useful indicator of DCS improvement. The primary hypotheses for the present study were that treatment response during exposure therapy would be enhanced by DCS administration and a behavioral measure of anxiety would provide utility in assessing outcomes. Both hypotheses were generally supported; however, the small sample size in this study, due in part to attrition, and large variability in responses warrant caution in interpretation of in the context of these limitations.

Study 2

Measures

Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987)—The LSAS, completed at the start of each session, is a 24-item scale assessing the range of social interaction and performance situations individuals with SAD may fear and/or avoid. Items are rated on a 0-3 Likert scale (with 0 being no fear/avoidance and 3 being severe fear/avoidance) with higher scores indicating greater distress. The LSAS demonstrates good reliability (Baker, Heinrichs, Kim, & Hofmann, 2002) and consistency (Heimberg et al., 1999). Chronbach's alpha score for the LSAS at the initial intake was .90. Cut-off scores of 50-60 are generally considered “probable” for likely SAD at a moderate level, and remission is often considered met at scores below 30.

Brief Fear of Negative Evaluation Scale (BFNE; Leary, 1983)—The BFNE was completed at the beginning of each session. It is a 12-item measure used to determine the degree of apprehension at the prospect of being evaluated negatively, rated on a Likert scale with 1 being “not at all characteristic of me” and 5 “extremely characteristic of me”. The BFNE has been shown good reliability, construct validity, and sensitivity to pre- and post-CBT changes (Collins, Westra, Dozois, & Stewart, 2005). Cronbach's alpha at session one was .85.

As in Study 1, a behavioral avoidance task (BAT) occurred immediately after each session, in the same manner as described above.

Session Protocol

All participants engaged in a maximum of 10 weekly, individual sessions conducted by doctoral graduate student therapists trained on the protocol. Phone consultation with the principal investigator was available to the study therapists. The protocol was adapted from an intervention by Hofmann & Otto (2008) and a similar version has been used in earlier

DCS studies (Hofmann et al, 2006). The first session was psycho-educational in nature, and therefore no formal exposure occurred nor was medication administered. Formal exposure trials began during the second session and continued until the final session. In vivo exposures were tailored to each participant's areas of anxiety, and occurred throughout the immediate community environment, utilizing confederates when relevant. Sessions consisted of in-session in vivo exposures, feedback, discussion and reaction to exercises with reference to the therapy model, weekly monitoring and discussion of self-exposure practices, discussion of obstacles, cognitive restructuring, and planning for out-of-session practices.

Medication administration algorithm—During in-session exposures, conducted for a minimum of 15 minutes, study therapists recorded participant SUDS at regular intervals. These SUDS scores, separate from the BAT SUDS ratings used as an outcome variable, were used to determine if in-session partial extinction learning had been achieved, and if the medication or placebo was to be administered. This was determined based on an administration algorithm developed by the researchers to determine “successful exposure.” Successful exposure was operationalized as a minimum decrease of two SUDS points from the highest or peak in-session SUDS rating to the final rating, with the final rating constant or continuing to decrease over the last two scores in the in-session exposure trial. In the event that SUDS ratings were low to begin with (precluding a decrease over the course of the exposure), a final SUDS rating of 2 or less was required. Participants who met these criteria received a medication or placebo pill, previously determined at initial randomization, at the end of the session,. Participants were not informed of the algorithm, nor were they told medication administration was dependent on their behavior. Rather, they were notified only that they “may or may not receive a pill following each session.” The use of the two point change requirement was informed by clinical experience and modest evidence reported in the literature concerning expectations of change within session (Hayes, Hope & Heimberg, 2014). These investigators reported a range of expected SUDS change in treating social anxiety from 1.61 – 2.70, an average of approximately 2.15 SUDS units for exposure trials. The terminal SUDS ratings were based on commonly used criteria for judging when asymptotic or near asymptotic SUDs levels have been reached, rather than the zero anchor proposed in Wolpe's 1990 anchors for SUDS (i.e. meaning that peace, serenity, and total relief of bad feelings of any kind has been achieved).

Results, Study 2

A total of 64 participants were assessed for eligibility. Of those, 24 qualified for the study based on the screening session. Sixteen entered treatment and were randomized into the study, and represent the ITT sample. Of the 16 who were randomized and entered treatment, seven were in the DCS group and nine in the placebo group. Detailed demographic information is presented in Table 1. There were no differences between groups on age ($p = .08$) or gender ($p = .72$), nor on symptom measures at pre-treatment (LSAS, $p = .62$; BFNE, $p = .37$), except for SUDS ratings ($p = .001$). Accordingly, SUDS scores at session 1 were controlled for in subsequent analyses.

Of participants who entered treatment, seven completed and nine dropped out prior to reaching termination criteria; all dropouts occurred at or prior to session 5, with half of the

dropouts occurring after the first two sessions. No differences were found between treatment completers and drop-outs on age ($p = .21$), gender ($p = .85$), or severity scores (based on the ADIS) at the eligibility assessment ($p = .38$). The dropout rate was high in both groups. However, the DCS group had fewer dropouts, and the two groups did not differ significantly in regards to dropout rate ($p = .62$, Fisher's exact test, two-sided). Response (decreases greater than the reliable change criterion on the LSAS) and remission (scores below the cutoff of 30 on the LSAS for minimal symptoms) rates showed that more DCS participants were considered treatment responders (57%) and remitters (43%) as compared to the placebo group (22% and 0%, respectively), although differences were only marginally significant per Fisher's exact test ($p = .30$, $p = .06$, respectively). Means and standard deviations are available in Supplemental Table 2 and graphs for each measure are presented in Figure 2. In the study, all participants achieved "successful" in-session extinction as determined by the study algorithm; therefore, all participants received DCS or pill placebo following every session. Thus, the resulting analyses consist of two groups who all received DCS or placebo following each session.

The linear mixed models for all measures improved in regards to fit with the addition of treatment group and session 1 SUDS scores for all measures (LSAS, $p = .03$; BFNE, $p = .01$; SUDS, $p = .01$). The primary measure of social anxiety, LSAS, evidenced a significant interaction, in favor of DCS ($F_{1,152} = 6.14$, $p = .01$, $d = 0.40$, 95% CI = .20-2.60). While the BFNE showed a significant main effect for time ($F_{1,9.7} = 5.68$, $p = .04$, $d = 1.15$, 95% CI = .02-2.21), there was no differential effect for group ($F_{2,9.7} = 1.09$, $p = .32$, $d = .52$, 95% CI = -.49-1.51). Session one SUDS scores significantly predicted outcome on that measure ($F_{1,15.7} = 31.57$, $p < .001$) but there was support for an interaction effect as well in favor of the DCS group over time ($F_{2,21} = 12.87$, $p = .002$, $d = 1.80$, 95% CI = .66-2.89).

Treatment compliance was rated at 100% for primary session components and 92% for exposures meeting the protocol length. Sessions with exposures slightly shorter than protocol length were included in analyses given that SUDS levels showed decreases that met the study algorithm.

Discussion, Study 2

The results of the present study were mixed, but somewhat support the study hypothesis, in that participants who received DCS appeared to benefit to a greater extent than those who received placebo on a measure of social anxiety, the LSAS. The SUDS measure shows evidence for a similar pattern; after statistical adjustment for initial differences on SUDS, participants who received DCS appeared to benefit to a greater extent than those who received placebo. Moreover, DCS participants were considered treatment responders and remitters at greater rates than the placebo group (57% vs. 22% responders, 22% vs. 0% remitters) per the LSAS. However, these rates were not statistically different. LSAS scores for the majority in the DCS group, although decreased and considered a positive response, were still within the symptomatic range. This suggests a caveat when interpreting clinical significance in the context of statistically significance findings.

The primary aim of the present study was to test the feasibility of administering DCS following sessions, contingent upon in-session learning. More recently, the benefit of post-

session administration has been discussed whereby administration based on the occurrence of in-session extinction may reduce the possibility of iatrogenic conditioning in the event of unsuccessful exposures. Study 2 carries the same limitation as Study 1 regarding small sample size and attrition. A limitation of Study 2 was posed by the absence of variability vis-a-vis participant-evidenced in-session extinction, resulting in no instances where a participant did not receive a pill (i.e., failed to show in-session learning). Thus, while feasibility of post-session administration could be determined more broadly, proof of concept regarding medication administration based on successful exposure specifically could not be assessed in the present study due to lack of participant variability in this connection.

General Discussion

The current paper presents two randomized double blind studies examining the differential effectiveness of DCS medication as an adjunct during exposure-based therapy. Although the small group sizes for analyses preclude definitive interpretation of conclusions, the results generally align with existing literature. The present studies contribute to the existing literature by examining a behavioral measure of outcome and the utility of a post-session administration strategy. Despite mixed findings in the DCS literature and general consensus from meta-analyses that there is either no difference between DCS and placebo on overall effectiveness, or at best, small to modest effects (Bontempo et al., 2012; Ori et al, 2015, Rodrigues et al., 2014), great interest and enthusiasm continues for the potential of DCS augmentation. From one perspective, this enthusiasm may be an example of publication bias in psychological sciences that has been increasingly noted in the field (Ferguson & Heene, 2012; Ioannidis, 2005). This can be particularly relevant for newer theoretical models or “hot” topics that persist past their utility through shifting assumptions (Ferguson & Heene, 2012). Such bias can be problematic with focus on statistical over clinical significant from single studies, and of smaller studies, (Ioannidis, 2005), of which the present study is an example. From another perspective, given the early stages of research in this field, non-replication or negative findings in some domains can help refine focus (e.g., administration strategies and particular populations). Indeed, this was illustrated by the work of Smits and colleagues examining successful exposure sessions (2013b) and that found that end fear, but not change in fear over the course of exposure, was a useful predictor (2013a). At the time of the present study design, this work was not yet published. From the perspective of the present study, given the importance of anxiety reduction during exposures, Study 2, in addition to evaluating the impact of DCS on exposure-based social anxiety treatment, also attempted to evaluate use of an algorithm-based administration strategy on self-reported and behaviorally assessed symptom reduction. To our knowledge this was the first study to test an administration strategy based on an in-session change algorithm. All participants met the criteria each session (a reduction in SUDS ratings of at least two points) and on average demonstrated treatment benefit. Thus, while the present work cannot critically evaluate full impact of dosing strategy due to lack of variability in the sample, it provides a model for future investigations. The post-session administration strategy was implemented as planned with fidelity and was tolerated by participants.

Investigations of DCS may be enhanced through use of biological and behavioral measures. In Study 1, participants were assessed on observer-rated behavioral measures of anxiety

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during a behavioral avoidance task. The results provide evidence that an overt, behavioral measure may be useful in assessing therapeutic change and, related to the above discussion may be particularly useful for determination of session success prior to DCS administration. The finding that the TBCL scores showed a slight increase in the context of level SUDS scores over time for the placebo group in Study 1 may be worth further examination in this respect. Future research should therefore examine whether behavioral measures or biomarkers are more sensitive to identifying in-session extinction learning when compared to a subjective measure. Indeed, Rothbaum and colleagues (2014) demonstrated evidence for physiological changes in favor of DCS in the absence of significant changes to subjective reports. We would argue that the use of a behavioral or physiological marker might be beneficial in the determination of a successful exposure session and have utility in post-session administration decisions.

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A number of limitations of the present investigation and points for future direction should be noted. Importantly, the sample size was small, affecting the power needed to best analyze some of the research questions, and preventing more detailed predictor analyses. Dropout rates were high in this study. While high attrition rates have occurred in DCS studies with different clinical populations (e.g., de Kleine et al., 2012), the rates were higher than other DCS studies of social anxiety disorder (e.g., Hofmann et al., 2013). High attrition rates of this study and others were also noted in the Cochrane review as being a potential source of study bias (Ori et al., 2015). In Study 1 participant attrition occurred primarily between the assessment and initial treatment sessions; thus, scheduling the first treatment session closer in time to the assessment, or combining these sessions may attenuate the likelihood of avoidance behavior and capitalize on participant motivation following assessment. In Study 2, the primary reason for dropout was scheduling difficulties. Greater attention to timing of treatment initiation or proactive scheduling may reduce this occurrence. Due to rates of dropout, follow up data was not available for examining maintenance of effects. Given the importance of generalizability and strengthening against relapse, future studies would benefit from examination of longer-term outcomes.

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Further research into post-session administration contingent on exposure success of DCS is likely already ongoing, and will provide valuable information about DCS enhancement effects with this method. Study 2 offers just one potential method for measuring in-session extinction utilizing an algorithm based on self-reported distress levels. How best to determine successful extinction remains an open question, but should be realized through further investigations that examine processes relevant to fear extinction (behavioral, genetic, and physiological). The determination of a successful session was used for medication administration decisions; the study was not designed examine successful vs. unsuccessful exposure session outcomes. Given that all participants were given study medication, this could not be explicitly examined. The lack of blinding of study therapists may have impacted the rates of “successful” exposure; however, given that study therapists did not know which condition participants were assigned to (DCS or Placebo), this likely mitigates the impact of potential therapist bias. The use of a third party to determine if the algorithm is achieved may impact rates of “successful exposure” and thus, rates of medication administration and therefore may be useful for future studies using an in-session or post-session determination. Study 1 investigated the utility of a behavioral indicator of anxiety

and provides an example of an alternative to subjective ratings that can be used to assess in-session anxiety. While the use of biological and behavioral measures of change in the DCS literature has lagged behind that of subjective measures, use of biomarkers of treatment response has been increasing (e.g., Rothbaum et al, 2014) and will undoubtedly inform about the efficacy of DCS administration for clinical purposes.

The present findings and clinical interpretations in this area more broadly should be viewed in light of mixed overall findings and with consideration of the potential for publication bias on interpretation of effects. Improving the quality of research and decreasing bias can be helped in general, with larger, better powered studies that contain less potential for bias (Ioannidis, 2005), and more specifically within DCS investigations, through disentangling the effects of extinction learning and level of fear, determining timing of administration, and use of more clinically relevant measures such as quality of life (Ori et al., 2015) with an eye toward “careful attention to clinical moderators” with the use of cognitive enhancers (Litz et al., 2012). It is hoped, however, that the present work highlights and serves as an illustration of the usefulness of two particular areas within the DCS literature: a post-session administration strategy and utility of behavioral measures that might be adopted by larger-scale efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Mean group scores ($n = 13$) for Study 1 outcome measures of Subjective Units of Distress and Timed Behavior Checklist. TBCL scores were not available for Session 1 due to experimenter error.

Figure 2.
Mean group scores for Study 2 outcomes measure (n = 16) of the Liebowitz Social Anxiety Scale, Subjective Units of Distress, and Brief Fear of Negative Evaluation.

Table 1

Participant characteristics by Study and Treatment Group.

Characteristic	N (%)					
	Study 1			Study 2		
	Total	DCS	Placebo	Total	DCS	Placebo
Sample size	N = 14	n = 7	n = 7	N = 16	n = 7	n = 9
Age, mean(SD)	20.11(2.02)	20.84(2.62)	19.39(0.90)	19.81(1.91)	19.00(1.12)	20.86(2.27)
Gender (female)	12 (86%)	6 (86%)	6 (86%)	10(63%)	6(67%)	4(57%)
Race/ethnicity*						
Caucasian	10 (71%)	5 (71%)	5 (71%)	10(63%)	5(56%)	5(71%)
Hispanic	--			2(16%)	2(25%)	2(25%)
African American	--			1(6%)	0	1(13%)
Other	4 (29%)	2 (29%)	2 (29%)	3(22%)	2(25%)	1(13%)
Completer status	13 (92%)	6 (86%)	7 (100%)	8 (50%)	5 (71%)	3 (33%)

* For study 1, race/ethnicity was only assessed as Caucasian vs. Other