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Slope of Change through D-Cycloserine Facilitation of Exposure Therapy in a Social Anxiety Population

Christina M. Sheerin
Western Michigan University, christina.sheerin@gmail.com

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SLOPE OF CHANGE THROUGH D-CYCLOSERINE FACILITATION OF EXPOSURE THERAPY IN A SOCIAL ANXIETY POPULATION

by

Christina M Sheerin

A dissertation submitted to the Graduate College in partial fulfillment of the requirements for the degree of Doctor of Philosophy
Department of Psychology
Western Michigan University
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Doctoral Committee:

C. Richard Spates, Ph.D., Chair
Scott Gaynor, Ph.D.
Lisa Baker, Ph.D.
Andrea Kozak, Ph. D.
The present study sought to add to a growing base of research investigating approaches that facilitate the therapeutic effects of exposure-based therapy for social anxiety disorders. In particular, the approach involves the use of medication adjuvants that work in conjunction with therapeutic learning. This work translates findings from preclinical work to further our understanding of the neurobiological mechanisms that impact extinction learning. Among others, a promising method has been found with the use of D-cycloserine (DCS), a partial NMDA receptor agonist. Evidence of its positive impact in preclinical work has led to its application to clinical populations who suffer from anxiety disorders. The present study aimed to add to the treatment outcome literature in this area. The study utilized a double-blind placebo-controlled design and a 10-session exposure-based CBT protocol with a participant population who met criteria for social anxiety disorder. The treatment protocol allowed for successful termination criteria to be reached following session 5, as well as deployed an algorithm that relied on in-session distress ratings to determine if sufficient learning occurred in each session. The latter was used as a determining factor for administration of the active versus inactive ingredient (placebo) immediately following each session. Changes were investigated using the administration of pre-session self-report measures and in-session
behavioral and process measures. Rate of treatment attrition, meeting early termination criteria, the comparative extent of changes on symptom measures early in treatment, and comparative extent of maintenance of gains comprised key indicators of outcome. Potential moderators of DCS’s effects were also investigated. Data were investigated using both Linear Mixed Modeling and single subject analyses to investigate the slope of change, the interaction of treatment over time, and to address process-related questions. Results showed some evidence of DCS enhancement, as seen by greater slopes of change and more stable change as compared to participants receiving placebo on some measures. These benefits were seen over the full course of therapy as opposed to early in treatment. Initial severity levels were implicated as potential moderators of treatment effect.
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CHAPTER I

PROJECT OVERVIEW AND INTRODUCTION

Overview

The present study aimed to expand upon the literature base of D-cycloserine (DCS) as an adjunct to exposure-based therapy for anxiety disorders by using a clinical population of socially anxious individuals. The study examined self-report, behavioral, and physiological dependent variables across sessions within the context of a double-blind, placebo-controlled randomized controlled trial. Potential participants from the Western Michigan University community were recruited for the study. Interested individuals were asked to attend an initial assessment meeting and screening with a collaborating psychiatrist in order to determine eligibility for the study. If eligible, participants were randomly assigned to receive either a DCS or placebo pill immediately following each treatment session. All participants received the same manualized treatment adapted from a full cognitive behavioral protocol for social anxiety disorder (Hofmann & Otto, 2008). The Anxiety Disorders Interview Schedule IV for DSM-IV (ADIS-IV) and the Leibowitz Social Anxiety Scale (LSAS) were administered during the assessment session to determine eligibility for the study. The following assessments were administered weekly (aside from the Social Phobia and Anxiety Inventory) and at follow-up sessions: Brief Fear of Negative Evaluation questionnaire (BFNE), Liebowitz Social Anxiety Scale (LSAS), Social Phobia and Anxiety Inventory (SPAI), Anxiety Sensitivity Index (ASI), State-Trait Anxiety Inventory (STAI), a measure of f-EMG
currogator reactivity, and a Behavioral Avoidance Test (BAT) with a public speaking task while using the Timed Behavior Checklist (TBCL). It was hypothesized that all participants would experience a decrease in speech anxiety as evidenced by reductions in SUDS ratings during the BAT, self-report symptom measures, and physiological arousal, with participants who received DCS evidencing greater improvement, potentially earlier in treatment.

**Introduction**

**Overview of Anxiety Disorders**

Anxiety disorders are common psychiatric disorders; indeed, within the United States they are the most prevalent of psychiatric disorders. About 30 million people will be affected by an anxiety disorder at some point in their lifetime, with some estimates reporting even higher rates (Ohayon, 2006). The World Health Organization predicts that by the year 2020 depressive and anxiety disorders combined will be the second leading cause of burden among all diseases. Regardless of the specific anxiety disorder, all anxiety disorders share similarities, such as physiological arousal, chronic apprehension, arousal related to the potential occurrence of future threat, and avoidance (American Psychiatric Association [APA], 2000).

**Overview of Social Anxiety Disorder**

According to the National Comorbidity Survey Replication, which provided lifetime prevalence rates of numerous mental disorders, social anxiety disorder had a lifetime prevalence rate of 12.1%, making it the second most common anxiety disorder (Kessler, Berglund, et al., 2005). The past-year prevalence rate of social anxiety disorder has been measured to be about 6.8% in American samples (Kessler, Chiu, Demler, &
According to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*), the core feature of Social Anxiety Disorder (SAD) is a marked and persistent fear of social or performance situations, linked to fears that the individual will be embarrassed or humiliated. Exposure to the social or performance situation reliably leads to an immediate anxiety response (APA, 2000). Individuals with social anxiety disorder typically avoid the feared situations due to marked anxiety or may force themselves to endure the situation while experiencing intense anxiety. Marked anticipatory anxiety may also occur far in advance of upcoming social or public situations. The variability in the breadth and severity of SAD can be great and can be characterized by differences in the developmental characteristics, chronicity, and disability consequences posed by symptoms (Hofmann & Otto, 2008). Among the many potential social fears, a particularly challenging one, relevant to the proposed study, is public speaking situations. While public speaking fears are common and exist independently from social phobia, most individuals with social anxiety disorder fear public speaking. To illustrate, it has been shown that social phobic individuals with a specific public speaking fear show greater anticipatory anxiety and greater heart rates compared to normal controls and generalized social phobics during a public speaking task (Blote, Kint, Miers, & Westenberg, 2009). Physical symptoms that often accompany social anxiety disorder, and that reliably occur in public speaking situations, include blushing, profuse sweating, trembling, nausea, and difficulty talking (NIMH, 2007). Common associated features include hypersensitivity to criticism, negative evaluation, or rejection; difficulty being assertive; low self-esteem; poor social skills; and underachievement in school (APA, 2000). Social anxiety disorder typically has an onset in the mid-teens (median age 16).
and is fairly equivalent across genders, with a frequently continuous course without treatment (APA, 2000).

**Treatment of Anxiety Disorders**

Despite the high prevalence rates of anxiety disorders, these problems are often under-treated and can be difficult to treat. Effective therapies for anxiety disorders are available, and research is still uncovering new treatments that lead to improvements in the lives of individuals. In general, anxiety disorders are treated with medication (most commonly benzodiazepines, monoamine oxidase inhibitors and selective-serotonin reuptake-inhibitors), specific types of psychotherapy, or both. Established psychotherapy for anxiety disorders generally falls within the domain of cognitive-behavioral therapy (CBT) and is quite effective in treating these disorders. Exposure is considered to be a crucial aspect of successful cognitive-behavioral treatment (Hofmann, 2007). Meta-analytic studies examining the relative importance of separate components in treatments for social anxiety disorder have shown that cognitive-behavioral and exclusively exposure-based treatments did not differ in drop-out rates and yielded similar effect sizes on post-treatment and follow-up measure of social anxiety, cognitive symptoms, and general anxiety (Feske & Chambless, 1995). A commonly used treatment for social anxiety disorder is based specifically on putting the client in contact with public speaking situations and requiring him or her to engage in public speaking behaviors. Public speaking is a useful focus because it is a valid exposure situation that can be easily modified and tailored for individuals. It has also been shown that treatments that specifically target public speaking anxiety generalize to other social fears and can have effects on more generalized social anxiety symptoms in a similar way as more
comprehensive treatments (Hofmann, 2004; Newman, Hofmann, Trabert, Roth, & Taylor, 1994). Exposure-based behavioral therapy has been used for many years; it allows the individual to gradually encounter the object or situation that is feared along with support and guidance from the therapist, leading to the development of new safety learning that inhibits the existing feared associations.

Exposure therapy is a notable achievement for the field of clinical psychology, and although these therapies are the most effective current forms of treatment for anxiety disorders, they can be improved in a number of ways. One area in need of improvement is the high level of treatment attrition. A substantial percentage of patients and participants fail to complete treatment, dropping out after a few sessions before improvements have been made. In addition, as discussed by Antony (2011), despite advances in the treatment of anxiety disorders, many who are treated respond partially or not at all. This has resulted in recent treatment research that focuses on trying to identify strategies for improving outcomes with existing treatments. Researchers are continually looking for ways to improve upon established interventions, resulting in many recent innovations in the field. With the high prevalence of anxiety disorders, these and other issues warrant research and clinical focus. As McNally discussed, further advances in treatment for anxiety disorders within the field will first require a better understanding of the mechanisms of fear and its reduction (McNally, 2007).

One attempt to improve treatment has focused on the potential benefit of combination-treatment strategies for anxiety disorders (i.e., use of tricyclics or benzodiazepines along with cognitive-behavioral therapy), although results have often been disappointing. Some studies show that although combined treatments may achieve
benefits over CBT alone in the acute treatment phase, these benefits do not seem to maintain, and potentially lead to a loss of efficacy when the medication is discontinued (Otto, Basden, Leyro, McHugh, & Hofmann, 2007; Otto, Smits, & Reese, 2005). A more novel approach, following from increased understanding of the mechanisms of fear reduction, has taken the concept of combined treatment in a novel direction. The use of D-cycloserine (DCS) to enhance therapeutic learning has helped establish a novel approach for combination treatment for the anxiety disorders. As discussed by Otto and colleagues (2007), in contrast to traditional combination treatment which involves pharmacotherapy provided concurrently with psychosocial intervention, DCS augmentation is used not for anxiolysis but for enhancement of the therapeutic learning offered by cognitive-behavioral treatments. In this application, it is administered in an acute dosing fashion along with exposure-based learning. This strategy and the theory and research behind its use and potential benefit will be discussed in the subsequent review.
CHAPTER II
LITERATURE REVIEW

Exposure Therapy and Extinction

The extinction process has been regarded as primarily responsible for the positive outcomes of exposure therapy in humans (e.g., Bouton, Mineka, & Barlow, 2001; Hofmann, 2007). In attempts to better understand the mechanisms at work in exposure therapy (i.e., extinction) and to improve its effectiveness, bridging the gap between clinical and preclinical research has become a recent goal. This has led to improved understanding behind the mechanism(s) of extinction and has been viewed as a particular success of translational research (Hofmann, Smits, Asnaani, Gutner, & Otto, 2011).

Both Pavlovian conditioned responses and instrumental responses are subject to extinction; however, the Pavlovian conditioned response will be addressed here. A major theme in the extinction literature is that while extinction (repeated pairings of the CS without the US) is procedurally simple, it is mechanistically complex, with underlying mechanisms such as attention modulation, habituation-like processes, contextual conditioning, modulation of the strength of associations between conditioned stimuli and response, and changes in the activation threshold of the unconditioned stimulus presentation taking on salience (Myers, Carlezon, & Davis, 2011). This extinction process is now generally considered to be a form of new learning, with similar, yet distinct processes as compared to the original fear conditioning. Like other forms of learning and memory, extinction involves encoding, consolidation, retrieval, and
expression phases mediated by different neural mechanisms (Myers et al., 2011).

Referring back to historical studies by Pavlov, it was found that extinguished conditioned responses could spontaneously recover and that reconditioning occurred faster than initial conditioning, which suggested that extinction is not erasure of the CS-US association, but is instead stored as a second form of memory. The memory for extinction is distinct from the memory of the initial fear conditioning (Santini, Muller, & Quirk, 2001). In line with this observation, other researchers have suggested that extinction is due to a devaluation of the US representation in memory (Rescorla, 1973), or to the learning of a competing association where the CS now predicts “no US” that interferes with the expression of the original CS-US association (Bouton, 1991). This implies that extinction training is a form of new learning in its own right, establishing an inhibitory association (CS-no-US). According to this perspective, the original CS-US association is still intact following extinction. Fear conditioning responses are long-lasting and resistant to forgetting, illustrated by the fact that without exposure to the conditioned stimulus in the absence of the unconditioned stimulus, the conditioned responses do not disappear. In contrast, extinction memory is a much more fragile, labile process that tends to reverse over time (Bermudo-Soriano, Perez-Rodriguez, Vaquero-Lorenzo, & Baca-Garcia, 2012; Myers et al., 2011).

The new learning concept better accounts for the findings that fear often returns following extinction, with the occurrence of such phenomena as spontaneous recovery, renewal, and reinstatement, which indicate that extinction does not undo the original learning. To illustrate, one well-established boundary condition of DCS effects on fear extinction is that it does not abolish the renewal effect (Vervliet, 2008), meaning, while it
can increase the rate at which the fear response decreases, fear is still renewed when the CS is returned to and tested in the original context. This suggests that although DCS administration can benefit therapy, it does not qualitatively change the nature of fear extinction learning, which remains relatively context-specific and vulnerable to relapse (Vurbic, Gold, & Bouton, 2011). Furthermore, though fear conditioning can suppress the fear-associated response, it does not seem to remove the synaptic changes acquired during fear conditioning (Bermudo-Soriano et al., 2012). The idea that extinction is considered a form of acquired inhibition that counteracts or suppresses fear responses that are no longer adaptive, i.e., “new learning,” is strongly supported by other research (Bouton, 2007; Davis, Myers, Ressler, & Rothbaum, 2005; Ledgerwood, Richardson, & Cranney, 2004; McNally, 2007).

**Neurobiological Mechanisms**

In the search for better understanding of the mechanisms at work in extinction, researchers have focused on concepts and findings from research in the field of neurobiology. At the neural level, studies have revealed similarities between the mechanisms of extinction and acquisition. Fear conditioning in humans, unlike animals, relies on both lower order and higher order processes. Although some disagree (Hofmann, 2004), it is generally assumed that Pavlovian extinction training is an “automatic, unconscious, and low-level process that is separate from higher-order cognitive processes” (Grillon, 2009). A direct, subcortical pathway to the amygdala that bypasses sensory cortices has been identified in humans, which provides a substrate for automatic fears that arise independent of cognitive control (Grillon, 2009). A model has been created in which interactions among the amygdala, medial prefrontal cortex (mPFC)
and hippocampus mediate extinction learning and memory and its modulation by context (Myers et al., 2011). The amygdala is critical for the storage of both conditioned fear and extinction, the hippocampus processes contextual information, and the mPFC is critical for the retrieval of extinction learning (Kaplan & Moore, 2011). The amygdala, particularly the basolateral complex (BLA) of the amygdala, is the foundation of the extinction process. Both encoding and consolidation of extinction memory can be modulated by intra-BLA infusions of a wide variety of drugs including neurotransmitter receptor agonists and antagonists (Myers et al., 2011).

Fear extinction takes place when inputs from the hippocampus and mPFC activate glutamatergic neurons in the BLA; in this process, fear extinction predominates over fear-conditioning when synaptic strengthening in this new circuit is able to produce an association, and its related response, that is strong enough to overcome the association from the pre-existing fear-conditioning and its circuitry (Bermudo-Soriano et al., 2012). Molecular mechanisms of conditioning in the hippocampus include N-methyl-d-aspartate (NMDA) glutamate receptor activation, protein synthesis, gene expression, and intracellular signaling triggered by the protein kinase A (PKA). Thus, previous studies have investigated these mechanisms in the extinction of memory and other types of aversive conditioning (Luft et al., 2006). Fear acquisition and extinction are also both dependent on NMDA receptors in the amygdala, L-type voltage-gated calcium channels, (Davis et al., 2005; Ledgerwood, Richardson, & Cranney, 2003; Walker, Ressler, Lu, & Davis, 2002) and may also require protein synthesis (Santini, Ge, Ren, de Ortiz, & Quirk, 2004). Further, at a molecular level, studies suggest that NMDA receptor activation increases brain-derived neurotrophic factor (BDNF) expression. This, and related data
suggest that there are important bidirectional interactions between BDNF and NMDA receptors, which may be key for fear extinction, although more studies are needed in this direction to further clarify this issue (Andero & Ressler, 2012).

The NMDA receptor is an excitatory amino acid receptor subtype and is located at synapses of glutamatergic neurons that are critically involved in learning. NMDA receptors are located throughout the brain and are implicated heavily in learning, memory, and experience-dependent forms of synaptic plasticity such as long-term potentiation (LTP) (Myers et al., 2011). The NMDA receptor was the first of the glutamate receptors to be implicated in extinction and continues to be the most thoroughly studied. NMDA receptor sites are distributed throughout the central nervous system, with several specific high-density regions, including the BLA, a region also strongly implicated in Pavlovian fear conditioning (Ledgerwood et al., 2003). Evidence of the role of NMDA in fear conditioning and learning suggests there are numerous neuronal targets for pharmacologic modulation of fear responses.

Based on the role of the glutamatergic system during extinction learning and evidence that NMDA receptor blockade impairs extinction, it was proposed that this system could be modulated during exposure therapy by enhancing the functioning of that receptor (Davis & Myers, 2002). Competitive NMDA receptor agonists usually cause excito-toxicity, leading to cell death. However, D-Cycloserine (DCS), a partial agonist, enhances excitatory neurotransmission mediated by NMDA receptor without causing neurotoxicity by binding to the strychnine-insensitive glycine recognition site of the NMDA receptor complex and increasing calcium influx (Andero & Ressler, 2012). DCS works similarly to D-serine, a chemical in the brain that is believed to bind to the same
site on the NMDA receptor (Davis et al., 2005). DCS has been shown to enhance learning and memory in several animal paradigms without producing neurotoxicity, facilitating NMDA receptor activity in a more limited manner (Walker et al., 2002). DCS acts at the glycine modulatory site on the NR1 NMDA receptor subunit (Myers et al., 2011). Activation of this site improves the ability of the NMDA receptor protein to move calcium, which initiates a variety of intracellular events that are critical for learning (Davis, Ressler, Rothbaum, & Richardson, 2006). DCS indirectly increases glutamatergic activity in previously “silent” synapses, and in this way may enhance fear extinction by enhancing neuroplasticity (Bermudo-Soriano et al., 2012). Recent studies suggest that when extinction takes place in the presence of DCS, there is additional depotentiation of the synapse on the glutamate output neurons in the amygdala (Mao, Lin, & Gean, 2008). As discussed by Krystal (2012), the ability of DCS to depotentiate the activation of circuits that have undergone functional enhancement in the context of fear learning may further enhance fear extinction by protecting against fear reinstatement.

Preclinical Findings

Numerous animal studies have been conducted supporting the idea of DCS facilitation of extinction. These studies have administered DCS to rats through systemic and intracranial infusions directly into the amygdala before or shortly after extinction sessions and have found that DCS facilitates extinction, leading to decreased startle and freezing responses in less sessions than rats receiving placebo injections (Ledgerwood et al., 2003, 2004, 2005; Myers, Ressler, & Davis, 2006; Santini et al., 2001; Walker et al., 2002). The first study to demonstrate the effects of DCS on extinction was published by Walker et al. (2002), who showed that DCS facilitated extinction; fear-potentiated startle
was significantly lower in rats injected with 15 and 30 mg/kg DCS before extinction training. A second experiment by this group demonstrated that the effect of DCS reflects a specific influence on extinction and not a more general effect on fear-potentiated startle, such as neurotoxic or anxiolytic drug effects. This finding was further supported by another study (Ledgerwood et al., 2005), with reduced conditioned freezing found only in DCS rats that had also received extinction training. Walker et al. (2002) also administered HA-966, an NMDA antagonist, concurrently with DCS, which prevented the extinction effects, demonstrated earlier, strongly suggesting that the effect of DCS was mediated by NMDA receptor interaction.

Many preclinical studies have since been conducted investigating the use of DCS with extinction procedures, and have continued to show strong results. Numerous studies have shown that the extinction-enhancement effect of DCS is still present 24 hours after administration (e.g., Ledgerwood et al., 2003; Walker et al., 2002). DCS has been associated with significant effect sizes, demonstrating a large and robust effect ($d = 1.19$) when added to fear extinction procedures (Norberg, Krystal, & Tolin, 2008), and preclinical investigations utilizing a rat model of PTSD (single prolonged stress, SPS) have also shown promise for this approach (Yamamoto et al., 2008). Several important aspects of DCS facilitation have been shown thus far. Administration of DCS immediately following extinction training has shown the same effects as when administered prior to training (Ledgerwood et al., 2003, 2005) supporting the idea that DCS facilitates consolidation rather than just the acquisition processes. DCS appears to impact the consolidation processes that begin to occur during extinction training but continue following the training. In addition, DCS-treated rats also show increased
generalization to different CSs compared placebo treated rats (Ledgerwood et al., 2005). Additional information has also been gained in regard to the timing of DCS-facilitated extinction following fear conditioning. Research has shown that although DCS facilitation is evident when extinction learning occurs 24 hours following fear conditioning, it does not facilitate leaning when extinction occurs immediately (10 minutes) following the fear conditioning itself or an additional stressor (footshocks). The authors (Langton & Richardson, 2010) discussed the importance of this knowledge for translating to clinical work, in that DCS may not be inappropriate for use during intervention treatments immediately following trauma.

Importantly, there are also notable boundaries on DCS enhancement. While DCS reduces the occurrence of spontaneous recovery and reinstatement, it does not impact fear renewal or reacquisition (Vervliet, 2008). Additionally, DCS does not alter the context-specificity of the safety learning and, hence, may not protect against relapse as much as originally hoped (Bermudo-Soriano et al., 2012). Therefore, while DCS may protect against the return of fear in some conditions, the effects are not apparent in all situations. Other limits on the effects of DCS lie in the dosing; it seems to lose its effects with repeated, chronic use. One study showed that the disruption of facilitation was proportional to the number or amount of pre-exposures, although with a period of drug-free days between pre-dosing and extinction training, the effects are restored (Parnas, Weber, & Richardson, 2005). It may be the case the pre-exposure to DCS abolishes its activity at the NMDA receptor (Parnas et al., 2005). DCS also does not seem to be effective during re-exposure, meaning that although it is effective for the first extinction process, when the fear is reinstated and then re-extinguished, DCS no longer shows
benefits over placebo (Langton & Richardson, 2010). However, given evidence that re-
extinction may be NMDA-independent, the lack of DCS effects may actually help to
strengthen the evidence of DCS activation at the NMDA site specifically. Additionally,
this is only the case when the same CS is re-conditioned and re-extinguished; when the
CS is new, DCS facilitation holds (Langton & Richardson, 2010). Important to the
translation to clinical work, DCS seems to only exert its effects for those animals who
showed evidence of extinction during the session; in fact, DCS led to an increase in fear
when it was combined with minimal exposure to the CS, suggesting that, in this case,
DCS may be enhancing memory “reconsolidation” when combined with minimal CS
exposure and extinction when combined with more exposure (Bouton, Vurbic, & Woods,
2008).

**Neuroimaging Findings**

Given the hypothesized neuronal mechanisms behind DCS’s effects, some
investigators have examined whether neuronal activity aligns with behavioral changes
that have been found. One study investigated the effects of DCS on brain activity during
exposure to phobic stimuli with spider phobic individuals and healthy controls (Aupperle
et al., 2009). These researchers found enhanced prefrontal cortex (PFC) and anterior
cingulate cortex (ACC) activation for phobic individuals receiving DCS. Although less
widespread, there was some evidence for enhanced ventral ACC activation in the healthy
controls receiving DCS. Another fMRI study utilized a Pavlovian fear conditioning
paradigm with electroshock to the finger (Kalisch et al., 2009). Results showed
significant treatment effects following training, with increased neural activity in the left
hippocampal region and right medial PFC, with trend-level significance in the amygdala region for those participants who received DCS.

While these studies utilized fear conditioning and not fear extinction paradigms, both align with preclinical research in the proposed neural regions of action. Additionally, the work by Kalisch and colleagues (2009) provided fMRI data that aligned with significant treatment effects seen in the physiological data (skin conductance). Aupperle and colleagues (2009) also discussed implications of the dorsal ACC involvement found in their study. This area is involved in cognitive processing and is important for the allocation of attentional resources, suggesting that DCS enhancement of these frontal regions may also reflect increased cognitive processing. This would align with the assertion of Hofmann (2004) that such higher level cognitive processes are crucial aspects of extinction and that may also be influenced by DCS facilitation. Further research of this nature will be crucial for supporting purported mechanisms of DCS action within specific brain regions and further elucidate its mechanism of action at a neural level.

**Clinical Implications**

The above findings can be interpreted as support for the assertion that DCS, through stimulating NMDA receptors, facilitates consolidation of a new memory that is acquired during extinction training (Richardson, Ledgerwood, & Cranney, 2004), and particularly the consolidation phase following extinction training. Importantly, as previously discussed, boundary conditions do exist that have implications in human populations and further point to the need for additional translational and clinical research. Regardless, the findings discussed above are not only important for improved
understanding of the extinction process, but they are significant from a clinical perspective and yield numerous implications. In clinical populations, it is thought that the reduced ability to extinguish intense fear memories and associations and prevent fear inhibition underlies clinical anxiety. This may contribute to the persistence of maladaptive fear and reduce the effectiveness of typical interventions (Davis et al., 2005; Walker et al., 2002). Exposure-based treatments, analogous to extinction procedures in animal paradigms, often rely on the progressive extinction of fear memories. Therefore, pharmacological enhancement of extinction could be of considerable clinical benefit.

As summarized in an editorial for *Biological Psychiatry* (Otto, 2002), after extinction training, memories of the original fear learning and the extinction (safety) learning are in competition, with the subsequent meaning of the fear cue (safety or danger) determined by the context in which it happens. Unfortunately, the second association learned (extinction) is not as strong as the original association and seems to be particularly dependent on context for retrieval. Additionally, it appears to be a more labile process than the initial fear conditioning. Therefore, in other contexts fear associations are likely to be stronger and take precedence over the extinction association. Contexts themselves appear to include such things as the physical environment or internal cues such as drugs or affective state. Changes in the internal state, such as anxiety reduction from an anxiolytic drug, may be a strong enough context that extinction (safety learning) is only maintained in that context, so when the drug is removed, so is the learned safety. Not surprisingly, as noted earlier, attempts to boost treatment response with combined CBT and pharmacotherapy have led to disappointing results (Hofmann et al., 2006). It has been proposed that, given the context specificity of extinction learning,
medications create a unique internal context, partly due to their ability to modulate affect along with side effects, which make it possible to discriminate their presence. This shift in internal context may lead to a loss of learned safety (Otto et al., 2007).

Based on such evidence, Otto and colleagues (2007) have proposed that to more effectively enhance exposure-based interventions for the anxiety disorders, effective pharmacotherapy should not have affect modulating or perceptible side effects and should be delivered in isolated-dosing strategies so that during therapy patients can achieve therapeutic learning independent of the medication, with the medication promoting the therapeutic learning of exposure-based CBT itself. Given this, the use of a minimal dose of DCS offered only in conjunction with treatment and in a time-limited manner, may be a particularly effective strategy. In addition to this strategy, care must be taken with its use in clinical populations, given the potential limiting conditions of DCS facilitation that have been noted in the preclinical research. For example, in addition to limiting dosing to acute use, administration should be limited to just a few sessions, to prevent a potential loss of effectiveness due to repeated dosing. Finally, based on evidence from preclinical studies (e.g., Bouton et al., 2008), it seems to be crucial that DCS is administered only when there is evidence that extinction learning has occurred in session, with the potential that its administration with sub-optimal exposure may actually lead to a reconsolidation of the fear memory instead of the extinction memory. Therefore, it may be best for administration to occur immediately following a session as opposed to prior to, and only administered when habituation has occurred. This would ensure that DCS is only administered if the necessary therapy conditions are met, as has
been discussed by numerous researchers (e.g., Bermudo-Soriano et al., 2012; Kaplan & Moore, 2011).

Although it is not fully understood at this point precisely how DCS facilitates extinction, several possible explanations have been proposed. One interpretation of the findings from preclinical research is that DCS facilitates extinction by enhancing the devaluation of the US representation, leaving the CS-US association still intact, but the CS activates a US representation that is too weak to elicit fear responses (Richardson et al., 2004). Another possibility is that DCS facilitates extinction by enhancing the learning of an inhibitory association, where the CS is associated with “no US” that can better compete with the original CS-US association for control over responding (Richardson et al., 2004).

**Translational Considerations**

It has been noted that in translating this research from preclinical to clinical populations, some obvious problems arise. In preclinical research the Pavlovian extinction model is easily measured, with observable elicited conditioned responses (i.e., freezing responses). However, in clinical population, the behavior that is measured is largely self-report data. There is an inherent and obvious difference between elicited responses such as freezing and responses emitted while giving a speech. Measuring operant behavior does not necessarily preclude the use of Pavlovian extinction as a valuable conceptual model, but it does require a caveat in interpreting data and discussing the model.

In considering these caveats, the dual model theory of fear conditioning (and extinction) is relevant to the use of DCS as a treatment adjunct (Rescorla & Wagner,
1972). This dual model describes two complementary defensive systems: the lower order, automatic process that is independent of conscious awareness, and a higher order cognitive system associated with conscious awareness of danger and anticipation. Grillon (2009) discussed the evidence that suggests that conditioning in rodents is essentially a low-level process, whereas laboratory-based conditioning procedures in humans rely on both this process and high-level cognitive learning. DCS may preferentially work on this lower-level learning, and therefore may similarly affect this aspect of the learning in exposure therapy. A critical issue in human exposure research involves the degree to which the CR depends on fast, automatic processes as opposed to more cognitive responses such as conscious thoughts and anticipation. Again, most likely, both are involved, but related to the present discussion, a direct subcortical pathway to the amygdala that bypasses sensory cortices has been identified in humans and provides a substrate for automatic fears that arise separately from cognitive control. As Grillon (2009) discussed, fear learning occurs through fear conditioning as well as vicarious conditioning and verbal information; preliminary evidence seems to show that automatic processes underpin fear and vicarious conditioning but not verbal information.

This focus on basic fear conditioning does not negate the importance of operant conditioning in this area, however. Dollard and Miller (1950) conceptualized anxiety in humans based on Mowrer’s (1950) two-factor theory. From this conceptualization, anxiety is established through respondent conditioning and maintained through operant conditioning. Meaning, fear is initially conditioned through respondent processes, which is followed by the development of avoidance responses. Fear and avoidance are maintained because the avoidance behavior is reinforced by termination of the
conditioned stimulus, which limits contact with the conditioned stimulus and thus opportunities for respondent extinction. Exposure therapies assume that both respondent and operant conditioning principles apply, and a goal of exposure-based interventions is to act upon the respondent component to allow for respondent extinction of conditioned fear responses. A second goal is to achieve operant extinction of conditioned avoidance responses, followed by successful approach behavior (Waller, 2004).

If this conceptualization is used, then it is assumed that both classical and operant conditioning are likely taking place, as one rarely happens in isolation from the other. Related to this, Skinner (1953) discussed the idea that “emotions” may not be reducible to a single class of responses or attributable to a single set of operations. Emotional expressions, or internal states, can be imitated by operant behavior (Skinner, 1953). When we measure broadly defined operant behavior such as giving a speech, we examine specific responses such as trembling, shaking, terminating the speech, etc. as co-occurring along with the respondent behaviors that are elicited by the speech environment (the CS). Unlike in animal paradigms, where the startle or freezing response can be clearly measured as unconditioned and conditioned responses, with humans, numerous additional behaviors are occurring. A complete account of anxiety or fear requires a description of the total behavioral repertoire pertinent to the specific learning context: reflex responses as well as expressions executed by the musculature of the face and body, an increase in the likelihood of escape behavior, and even verbal behavior (Skinner, 1953). It is assumed that the self-report assessments are measuring verbal behavior, which is hoped to mirror internal respondent states. In the present study, operant behaviors were measured with the assumption that they are occurring along with other
responses in the individual’s repertoire, i.e. conditioned elicited responses, and that as one class of responses is changing, so is the other. The proposed study measured outward behavioral indices of anxiety. While not directly parallel to the CRs (i.e., freezing) of rats in the animal models, these indices are believed to be correlates of respondent behavior, and therefore retain their usefulness as measurable behavior. In addition, physiological measures such as skin conductance and facial corrugator muscles can be used to provide a measure of more automatic, physiological responses. Generally speaking, this conceptual issue is one that has not been sufficiently addressed in the DCS studies of clinical populations. This matter is one that will require attention as the literature progresses.

**Facilitation of Pavlovian vs. Operant Conditioning**

In line with the above discussion, some work has been done to begin to elucidate the effects of DCS on respondent versus operant behavior. While both operant and respondent extinction are important for safety learning, the effects of DCS on these separate processes appears to differ. Although systematic research on the effects of DCS on the extinction of operant behavior is limited, some research to date has addressed the effects of DCS on classical vs. operant conditioning. As noted by Vurbic et al. (2011), while several studies investigating extinction of conditioned drug cues had begun to suggest that DCS can facilitate operant extinction under some conditions (e.g., Nic Dhonnchadha et al., 2010; Shaw et al., 2009), all of these studies included extinction to a CS cue that had been associated with the reinforcer in addition to extinction of the operant response itself. Through multiple experiments, Vurbic and colleagues (2011) presented data on designs to assess operant conditioning independently of any classical
conditioning, resulting in no enhanced effects of DCS on extinction of operant responding. The authors discussed that these results, combined with the rest of the literature, suggest that DCS may facilitate extinction when classical (stimulus-outcome), but not purely operant (response-outcome), extinction processes can play a role. This would align with evidence of the specific effects on lower-order, automatic processes as noted earlier.

**Clinical Findings**

Regardless of precisely how DCS facilitates extinction learning, empirical findings within the preclinical literature are important with regards to clinical anxiety populations. As discussed earlier, despite the efficacy of different exposure therapies, treatment attrition continues to be quite high. Additionally, some clients do not benefit fully from treatment, with some experiencing symptoms in different contexts, others experiencing a return of fears following an additional fearful or stressful event after treatment, and others considered non-responders to treatment. DCS may be particularly helpful for addressing these treatment limitations. In general, if DCS can speed up the process of extinction and reduce the number of sessions required, then fewer patients may fail to complete treatment. Seeing benefits earlier in treatment may increase motivation to stay in therapy, and support longer-term maintenance of gains. Additionally, if DCS can strengthen the learning process, it may be useful for non-responders, or slow responders, of exposure-based therapy. Given the potential clinical significance of DCS, several investigations have been completed to date to test the effects of DCS in human populations.
Researchers have investigated the use of DCS with the spectrum of anxiety disorders, including specific phobias, social anxiety disorder, panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder. The first clinical study to investigate the effects of DCS on exposure therapy conducted virtual reality exposure therapy with acrophobic individuals (Ressler et al., 2004). Participants were given doses of DCS (50 mg or 500mg) or placebo in pill form two hours prior to each of two sessions. Consistent with animal research, DCS did not affect the baseline level of fear, as seen in ratings during the first session. The effects of DCS were evident during the second session, and DCS participants (receiving either dose) experienced lower SUDS and spontaneous fluctuations of skin conductance than the placebo group and voluntarily elevated to higher floors in the VR simulation. In a three-month follow-up, results were maintained.

Following multiple investigations examining the use of DCS in clinical populations, a meta-analysis reported significant, moderate effect sizes of DCS versus placebo in clinical populations when added to exposure therapy for acrophobia, social anxiety, OCD, and panic disorder (Norberg et al., 2008). Although greater effect sizes based on magnitude of response have been found in the preclinical studies as compared to clinical populations, a majority of the studies indicate that DCS does indeed lead to an increase in exposure therapy’s efficacy. While more recent research findings have been somewhat variable, DCS adjunct use remains a promising method. More recent studies have provided additional information regarding the course of DCS facilitation and its limitations. In one notable paper (Chasson et al., 2010), which represents a re-analysis of null findings overall (Wilhelm et al., 2008), it was found that in the early stages of
treatment, DCS led to improvements at a much faster rate than exposure therapy without DCS, creating a six-fold advantage for DCS in the first half of an exposure and response prevention protocol for OCD. Although no significant differences were found by the end of treatment, the authors suggested that this does not necessarily mean that DCS stops working but that it may become redundant, possibly because it may have already exhausted its maximum utility (Chasson et al., 2010). Siegmund and colleagues (2011) found differential effects for a subset of individuals, with those with more severe panic disorder symptoms at intake showing significantly more improvement with the addition of DCS, as well as evidence for early change as opposed to change overall. Similarly, in the first study to investigate the use of DCS along with PE for PTSD, while no significant interaction effects were found, participants in the DCS group were more likely to show response than those in the placebo group. Notably, DCS enhanced outcomes in a subgroup of participants who took longer to show improvements (de Kleine, Hendricks, Kusters, Broekman, & van Minnen, 2012). Similar to Chasson and colleagues (2010), given their findings, these writers posited that for PTSD patients who respond well and quickly, ceiling effects may exist and DCS may not provide additional benefit. However, patients who fail to respond at first may benefit from pharmacologic augmentation. For these patients, the addition of DCS was indeed effective. Preliminary research has also been conducted, in a case series design, with DCS used for treatment non-responders of prior exposure and response prevention (ERP) for OCD (Norberg, Gilliam, Villavicencio, Pearlson, & Tolin, 2011). In this study, patients who had not benefited from ERP and SSRIs demonstrated significant improvements in OCD symptoms when DCS was added. While one participant showed significant treatment effects early, maintained at follow-up,
the other participant did not evidence a decrease in symptoms until after the fourth session, as opposed to early in treatment as expected. These authors suggested that DCS effects may not be limited to the first few sessions for individuals who do not easily respond to ERP. Such findings support future randomized controlled trials with non-responder populations.

Despite promising findings of numerous studies, others have not found such positive results, but nevertheless provide important information. A DCS analogue study using conditioned fear failed to show any benefits of DCS augmentation of placebo (Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007). However, as discussed by the authors, the use of a non-clinical sample may be a source for discrepant results, as well as the potential that higher-order conditioning was at the basis of the learned associations to the conditioned fear, and that the extinction of this fear may not rely on mechanisms that DCS acts upon, as previously discussed (Grillon, 2009). In addition, another study using one session of exposure therapy for spider fear (Guastella, Dadds, Lovibond, Mitchell, & Richardson, 2007) also found no significant differences with DCS augmentation. One potential reason for the lack of results offered by the authors was, again, the use of a non-clinical sample. It may be that the mechanisms at work are different or more sensitive to the effects of DCS in clinical-level fears. This would be supported by evidence discussed earlier regarding differential effects for a more severe subset of participants.

Crucial information has been gathered from other null findings and subsequent re-analyses of more recent studies with clinical populations. As discussed earlier, preclinical research has shown that DCS should be administered following successful extinction
learning to prevent the potential for fear reconsolidation to be strengthened. The first study to investigate DCS administration following treatment resulted in null results for DCS facilitation in a height phobia population (Tart, Handelsman, & DeBoer, 2013). Of note, however, the authors did not administer the medication based on evidence of in-session learning. The authors posited that such results may have been due to inadequate extinction learning in session. Therefore, the investigators (Smits et al., 2013) conducted a re-analysis of the data to examine whether the effects of post-session DCS administration on clinical outcome was mediated by response to exposure in session. In the re-analysis, fear ratings provided just before concluding the exposure exercise in session were used as an index of exposure success. It was found that for participants showing an end fear of zero, those receiving DCS were rated almost one full point more improved on the Clinician Global Impression Scale (CGI) than those receiving placebo. For participants who reported end fear at one standard deviation above the mean of the sample, those who received DCS were rated almost a full point less improved on the CGI. Such results were consistent with the idea that DCS enhances retention of whatever emotional learning occurred during the session. In further support of the importance of in-session exposure learning as a mediator of DCS effects, Litz and colleagues (2012) reported null results for DCS facilitation with a PTSD population, using post-session administration. The investigation resulted in the placebo group significantly outperforming DCS, with three participants reporting worsening of symptoms, all within the DCS group. Post-hoc analyses conducted of SUDS ratings at each session found that while there were no significant group differences in within-session decrements during the first exposure session, there was less of a decrease in SUDS in the DCS condition during
the third and fourth exposure sessions, with a trend evidenced in the second session. Given evidence of greater fear, assumed to reflect less in-session extinction learning, the authors posited that one explanation for their findings was the possibility that DCS inadvertently enhanced reconsolidation of the trauma memory.

As the authors of both investigations discussed, DCS can exert its desired effects when applied after a successful exposure session, but when combined with inadequate extinction learning, it can interfere with exposure therapy. As discussed by Litz and colleagues (2012), for extinction and reconsolidation to work together optimally, extinction learning needs to occur, and while the re-activated memory is in its labile state, reconsolidation would then be of a therapeutically updated memory associated with a decrease in fear. Similarly, Smits and colleagues (2013) noted that in their re-analysis, when end fear was low (extinction learning high), participants who received DCS exhibited significantly greater improvements in symptoms, whereas when end fear was higher (less extinction learning occurred), participants who received DCS showed less subsequent improvements. They suggested that such findings may provide a context for understanding the mixed results with respect to the efficacy of pre-session administration of DCS for anxiety disorders, in that weak or null effects may be due to large individual variability in fear extinction in session. These authors provided support for the decision to administer DCS post-session being made in relation to the degree of exposure success achieved during each session by each patient.

**DCS Facilitation in Other Domains**

While beyond the scope of the present investigation, it is worth briefly noting other areas where DCS has been investigated, in both preclinical and clinical domains.
Preclinical investigations have utilized DCS in conditioned taste aversion (see Mickley et al., 2012) and incentive downshift events (Norris, Ortega, & Papini, 2011), both of which are related to the retrieval of aversive emotional memory. Studies in this area indicate preliminary evidence that DCS facilitates consolidation of this type of learning. Similar to anxiety work, the effect of DCS was also shown to be restricted to acute and not chronic administration (Mickley et al., 2012). DCS has also been used increasingly in the field of substance dependence, primarily in animal models to date, to investigate facilitative effects on the extinction of conditioned stimuli associated with drugs and drug effects (see Myers & Carlezon, 2012, for a review). While results have been mixed at times, there has been some success in both animal literature noted above as well as with human clinical populations (see Santa Ana et al., 2009).

In clinical domains, DCS has been applied to other methods of anxiety treatment as well as to other forms of learning. In the field of attentional training, a result of translational research work itself, DCS has been investigated as a method of improving the new learning associated with these tasks. Attentional training itself has been shown to reduce attentional bias to threat cues as well as result in positive effects on behavioral indices of anxiety. In a study investigating the use of DCS facilitation of this training (Behar, McHugh, Peckham, & Otto, 2010), the authors reported preliminary evidence for a facilitating effect of DCS. While there was a significant decrease in attentional bias for DCS participants, with a large effect size, this difference was not associated with reactivity, or state anxiety, to emotional stress tasks.

Finally, there is an emerging interest in the field suggesting that DCS effects might be expanded to the enhancement of certain social behaviors, in the area of social
learning. Researchers (Modi & Young, 2011) have shown enhancement of the formation of social bonds in animals. The authors suggested that the mechanism of action in this area lies in the facilitation of oxytocin and the role of social memory. However, in a review, Otto (2011) noted that while this may be the mechanism of action in this paradigm, he suggested that DCS may instead be influencing the rate of habituation to a novel social stimulus. This would relate more to the understood effects of DCS on fear extinction, in that it may enhance acquisition of social comfort in response to novel social cues or contexts. Future research in these areas, while having implications for therapeutic work in different domains, is also extremely important for continued understanding of the mechanisms of action of DCS as well as the mechanisms at work in areas such as social learning or extinction of drug cues.

Conclusions

The information detailed above provides a sampling of the ongoing investigations of DCS facilitation of exposure-based therapy. Such work, in addition to furthering the field’s theoretical understanding of the extinction process, has implications for future directions of continued DCS investigations. Some factors seem to be necessary for DCS to have its effect: in-session extinction learning should be evident, dosing should remain acute, and likely limited in number (and preferably administered immediately following the successful exposure session), and higher clinical levels of anxiety may be warranted for its use to be indicated. Additionally, findings of increased speed of initial effects, as opposed to overall improvement, need to be further investigated, as well as the potential benefits for treatment non-responders. The use of more automatic, physiological measures may add clarity to the idea of whether DCS effects lower order as opposed to
higher order extinction processes. While DCS augmentation may prove to be beneficial in practice, much more must be understood and uncovered about the facilitory effects of DCS and its limitations before widespread use should be considered. As discussed by Antony (2011), researchers must be cautious about the potential for enthusiasm for emerging treatments that can often be greater than warranted by the available data, at the expense of established interventions. Such cautions are useful to keep in mind as research in the domain of DCS facilitation continues to develop.
CHAPTER III

PROBLEM STATEMENT AND THE PRESENT STUDY

Despite the increasing evidence base in the area of DCS facilitation, many ongoing and recently proposed questions are in need of additional investigation and support, such as:

1. Will administration of DCS following exposure therapy and with evidence of habituation in session fit with preclinical data and result in similar effects as found with administration prior to exposure?

2. At what point in treatment is DCS having the strongest effect, and is this effect seen in the earlier few sessions leading to increased speed of treatment gains?

3. Will physiological measures of more automatic responses align with the evidence of self-report measures of DCS effects?

4. Does the addition of DCS provide incremental validity over exposure therapy alone given the additional considerations needed for its use?

The Present Study

To address these questions, this study investigated the effects of DCS on exposure therapy for social anxiety disorder, with a population with clinical levels of anxiety and utilized a full treatment protocol. Social anxiety disorder lends itself well to the present investigation because it generally takes several sessions to achieve clinically significant improvements, allowing for several points of measurement throughout treatment as well.
as early termination criteria. Two published studies (Guastella et al., 2008; Hofmann et al., 2008) and one thesis study, have previously been conducted with this population, allowing the present study to add to a growing evidence base of DCS in general and with this population in particular. This study sought to extend previous research by including observable behavioral responses to supplement self-report measures. In addition, DCS is administered only after successful sessions, based on distress levels measured during in-session exposures, making use of information gleaned from preclinical research findings.
CHAPTER IV

METHOD

Participants

Twenty-four participants between the ages of 18 and 99 were recruited to participate in the study from the campus community. Flyers (Appendix A) were posted around the campus with relevant information about the nature of the study, what types of participants were being recruited, who was conducting the study, who to contact for more information, and information needed to schedule an initial assessment.

Inclusion criteria included those participants who met criteria for a current DSM-IV diagnosis of social anxiety disorder as evaluated using the Anxiety Disorders Interview Schedule (ADIS), supported by results of the Liebowitz Social Anxiety Scale (LSAS), with a minimum score required for designation of moderate social anxiety. All participants engaged in up to 10 weekly, one-hour individual therapy sessions with a protocol-trained doctoral level graduate student therapist with a minimum of one year of supervised clinical experience. The therapy sessions were adapted from a Cognitive Behavioral treatment protocol that focuses on in vivo exposures in each treatment session (Hofmann & Otto, 2008). Exclusion criteria included current major depressive episode, obsessive-compulsive disorder, panic disorder, and post-traumatic stress disorder, as well as diagnosis of bipolar disorder or psychosis, assessed by the ADIS-IV. The treatment protocol specifically targets public speaking fears of individuals with social anxiety disorder, and the above disorders were excluded as they may have hindered treatment, by
interfering with effects of exposure or prevented the participant from fully engaging in session. As determined during a medical screening (Appendix I), potential participants were also excluded if they were currently taking anti-anxiety or anti-depressant medications, currently using illicit substances, or on a medication that could potentially interact with DCS. Additionally, anyone with a drug allergy that included medications in the class with DCS was excluded for health reasons, as well as anyone who was pregnant (determined by pregnancy test given at the initial screening), breast feeding, or had medical conditions contraindicated for the experimental drug (e.g., a heart condition or epilepsy). All participating individuals were screened for current medications at each session to prevent any negative effects of a drug interaction. Also, individuals who reported currently drinking alcohol on a daily basis were excluded, as alcohol can have negative interactions with DCS. The medical screening portion of the initial assessment was conducted by a board-certified physician and collaborating investigator, Dr. Bangalore Ramesh, prior to randomization and initiation of treatment sessions.

**Setting**

All self-report assessment measures, therapy sessions, fEMG recordings, and behavioral avoidance tests were conducted in therapy room A within the Anxiety Disorders Laboratory in room 2502 of Wood Hall. The behavioral avoidance tests consisted of a mock public speaking situation. This required an impromptu speech, in the therapy room set up with a podium and chairs for an “audience,” which consisted of the therapist and other research assistants. These behavioral avoidance tests were taped for purposes of scoring the Timed Behavior Checklist. The medication and placebo pills were obtained in pill form from Sindecuse pharmacy and stored in individual bottles in a
locked cabinet within the research lab. The medication was administered immediately following the completion of the therapy session if the therapist determined that evidence of some extinction learning occurred during the session, as determined by an algorithm for in-session SUDS ratings, discussed in more detail later in the document.

**Materials**

**Anxiety Disorders Inventory Schedule for DSM-IV (ADIS-IV)**

The ADIS-IV (Brown, DiNardo, & Barlow, 1994) is a semi-structured interview that is used primarily for differential diagnoses of anxiety disorders along with severity ratings of distress and avoidance on a 0–8 scale. The ADIS includes binary and dimensional items, allowing for a diagnosis that follows with the DSM and also helps the clinician/researcher determine the severity of current symptoms. The principal diagnostic categories show good to excellent reliability, with the kappa coefficients for reliability with social anxiety disorder, specifically, of 0.77 (DiNardo, Moras, Barlow, Rapee, & Brown, 1993). The ADIS was administered at the screening session to determine eligibility for the study.

**Liebowitz Social Anxiety Scale (LSAS)**

The Liebowitz Social Anxiety Scale (Liebowitz, 1987) is a clinician-administered questionnaire that takes approximately 10–15 minutes to administer and aims to assess the range of social interaction and performance situations that individuals with social anxiety disorder may fear and/or avoid. It is also used to evaluate the efficiency of different social anxiety disorder treatments. The scale consists of 24 items that depict different social situations and the clinician is asked to rate the participant’s level of fear on a 4-point Likert scale. The LSAS is further divided into two subscales for scoring:
social interaction and performance situations. The reliability of all subscales of the LSAS is good, being 0.79 or higher, except for the fear ratings of the performance subscale, which was found to be 0.53. Internal consistency for all subscales has also been found to be high, once again with coefficients of 0.79 or higher. The LSAS has also been found to have good convergent validity with other measures of social anxiety and be sensitive to treatment change (Heimberg et al., 1999). The LSAS was administered at the screening session to determine initial eligibility for the study (minimum score of 55 indicating moderate social anxiety symptoms) as well as at the beginning of each session. In the present study, the Cronbach’s alpha for this measure was 0.91.

**Anxiety Sensitivity Index (ASI)**

The ASI is a 16-item self-report measure that is the most widely used assessment to measure the construct of anxiety sensitivity, defined as the fear of arousal-related sensations that arise from beliefs that these sensations have harmful consequences. The ASI requests respondents to rate the 16 items on a scale of 0 (very little) to 4 (very much) based on their own experiences. The ASI has been shown by previous studies to have acceptable reliability and validity (e.g., Reiss, Peterson, Gursky, & McNally, 1986). The ASI was administered at the beginning of each session. In the present study, the Cronbach’s alpha for the ASI was 0.78.

**State-Trait Anxiety Inventory (STAI)**

The STAI (Spielberger, 1983) is a self-report measure that assesses both enduring and transient characteristics of an individual, and takes about 5–10 minutes to complete. The STAI-State assesses how responders feel “right now, at this moment.” Individuals rate, on a 4-point Likert-type scale, how true each statement is for him or her, ranging
from “not at all” to “very much so.” The STAI has been shown to have excellent internal consistency (0.89) and excellent test-retest reliability (0.70) (Barnes, Harp, & Jung, 2002). The STAI was administered at the beginning of each session. In this study, the Cronbach’s alpha for the STAI was 0.91.

**Brief Fear of Negative Evaluations Scale (BFNE)**

The BFNE is a 12-item Likert-scale self-report questionnaire, shortened from the 30-item original version, the Fear of Negative Evaluation (FNE). The BFNE is the measure used most commonly to determine the degree to which people experience apprehension at the prospect of being evaluated negatively. People who score high on the scale tend to behave in ways designed to avoid the prospect of being evaluated unfavorably. The BFNE has a test-retest reliability of 0.75, comparable to the FNE, at 0.68. More recent studies have supported the construct validity of the BFNE and it has been shown to be sensitive to pre- and post-CBT changes in both social anxiety and panic disorder (Collins, Westra, Dozois, & Stewart, 2005). The BFNE was administered at the beginning of each session. In the present study, the Cronbach’s alpha for this measure was 0.85.

**Social Phobia and Anxiety (SPAI)**

The LSAS (Turner, Beidel, Dancu, & Stanley, 1989) is a 45-item self-report questionnaire that was empirically developed to be a specific measure of social phobia and includes somatic, cognitive, and behavioral aspects of social phobia. Each item is rated on a 7-point scale for frequency. Both subscales of the SPAI (social phobia and agoraphobia) have been shown to be internally consistent (ranging from .94 to .96) with test-retest reliability over two weeks of .86. The SPAI has been shown to be significantly
correlated with other self-report measures of social anxiety (ranging from .41 to .77).

The SPAI was administered at the session one and the final session (depending on when termination criteria were met). In this study, the Cronbach’s alpha for this measure was 0.92.

**Behavioral Avoidance Test (BAT)**

The avoidance task consisted of a mock public speaking situation. It was conducted at the end of each session in the therapy room which was set up with a podium and chairs for an “audience” consisting of the therapist and other research assistants. The participant was given a topic to speak on, and given three minutes to prepare. The participant was instructed to give a speech on the topic for at least 30 seconds and encouraged to continue the speech as long as he or she was able, with a maximum of five minutes. The BAT was conducted to measure SUDS and TBCL scores. SUDS ratings were recorded at the beginning, mid-way through, and at the end of the BAT (the impromptu speech). The BAT was also tape recorded for scoring the TBCL.

**Timed Behavior Checklist (TBCL)**

The TBCL (Paul, 1966) is an instrument that lists 20 observable manifestations of anxiety including behaviors such as swaying, arms rigid, extraneous arm and hand movement, voice quivers, etc. The BAT speeches were recorded and viewed by two trained research assistants. Behaviors were scored for either presence or absence during 30-second intervals. Raters observed and scored independently and then compared for agreement. The total TBCL score for each speech was derived by pooling the total occurrence of the behaviors for the first two minutes of each speech, with scores prorated if needed (if speeches were less than two minutes).
Subjective Units of Distress (SUDS)

The SUDS scale (Appendix F) is a self-reported rating scale of an individual’s feelings of anxiety/distress. Ratings are made on a scale of 1–10, with 1 referring to no anxiety at all, and 10 referring to the most anxiety that can be experienced/endured. SUDS scores were recorded at the beginning, middle, and end of each BAT; ratings were averaged to determine a single score per speech.

Facial Electromyography (fEMG)

f-EMG is a valence-specific measure of affect that assesses the electrical activity of the spontaneous or reflexive movements of specific facial muscles (Rotteveel, de Groot, Geutskens, & Phaf, 2001). It detects minimal differences in specific muscle activity even in absence of an overtly visible expression. Facial EMG measures of the musculus zygomaticus for smiling and the musculus corrugator supercilii for frowning have been useful in the measurement of valenced states (Rotteveel et al., 2001). For this experiment, GS27 pre-gelled disposable fEMG electrodes and the Procomp 2 with BioGraph Infiniti software (from Bio-Medical Instruments) was used for data acquisition and display. Facial EMG measure for negative emotions was conducted immediately following each session and prior to the BAT. The fEMG measures were recorded via small electrode pads placed near participants’ inner left eyebrow. Facial EMG was used in this investigation to permit a more discriminating, objective measure of “negative” emotion as a dependent measure of arousal.

Procedure

Interested individuals emailed the contact number provided on recruitment flyers or during classroom recruitments (see Appendix B). These participants were then
contacted via phone by the investigator. The researcher described the study using the script provided (Appendix C), and if the individual was interested, a screening assessment was scheduled. At the beginning of the screening session, each potential participant was given information on confidentiality and informed consent was provided, as well as detailed information on the medication being investigated in the study. The independent assessor read aloud the informed consent document and drug information handout (Appendix D), and then provided copies for the potential participant to read. If the individual consented to participate in the study, two signatures were required for each handout, with a copy of each given to the individual and another retained by the researcher and stored in a locked file drawer in the study laboratory, separate from the participant’s file and master list with ID number.

During the initial screening, the ADIS-IV was conducted by the independent assessor along with social anxiety measures to determine eligibility and rule out exclusion criteria. Specific social anxiety measures were completed to determine if the present treatment protocol would be an appropriate fit for the participant; a minimum score on the LSAS of 55 for moderate social anxiety was required for qualification. If the participant qualified based on symptom measures, the medical screening was conducted by a board-certified psychiatrist who volunteered his services for the present study. All potential participants met individually with the study psychiatrist for a medical screening conducted in the same therapy room as all assessments and sessions. During this meeting, he obtained a complete history and administered the patient-screening document to assess for conditions such as potential allergy, epilepsy, drug interactions, and pregnancy/breast-feeding (Appendix I). In addition, female potential participants
were required to take a pregnancy test. If participants qualified based on the medication screening, the psychiatrist once again obtained informed consent (following additional information given about the medication and potential side effects), and provided the participant with a means of contacting him in case of emergencies, and/or if any negative side effects were experienced. Females who agreed to participate were also required to take a pregnancy test mid-way through treatment.

Following this screening, and once consent was re-obtained, the medication was prescribed. Participants were randomly assigned to either receive a 250 mg DCS pill or a pill placebo. Participants had a 50/50 chance of receiving either the research study drug or placebo. A random number generator was used to randomly assign participants to one of two conditions. All participants, research assistants, and therapists were blind to the condition; however, the psychiatrist and pharmacy staff retained a list of all participants and those who were receiving DCS and placebo. In the only study to examine dose effects of DCS (Ressler et al., 2004), no significant differences were found between the effects of 50 mg vs. 500 mg DCS. Most of the previously discussed studies have used dosages of 50–150 mg of DCS. However, DCS is currently available from the Eli Lilly Company, under the brand name Seromycin, as a 250 mg pill. This dose was used in the current study in order to maintain the integrity of the medication and ensure accurate dosage and bioavailability of the medication.

All participants engaged in a maximum of 10 weekly, individual sessions. Sessions were conducted by doctoral graduate student therapists with a minimum of one year of supervised clinical experience who were trained on the protocol (adapted from Hofmann & Otto, 2008). Phone consultation was available to the study therapists. The
first session was psycho-educational in nature, and therefore no exposure occurred and no medication was administered. Formal exposure trials began during the second session, and continued until the final session. Before each session, research assistants administered the following assessment measures: LSAS, ASI, BFNE, and STAI; the SPAI was administered at pre-selected sessions. Sessions consisted of in-session in vivo exposures, feedback, discussion and reaction of exercises with reference to the therapy model, weekly monitoring and discussion of self-exposure practices, discussion of obstacles to practice, cognitive restructuring where relevant, and planning for out-of-session practices. During in-session exposures, conducted for a minimum of 15 minutes, study therapists recorded SUDS at regular intervals. These ratings were used to determine if in-session extinction learning had been achieved. This was determined based on an algorithm that required a minimum decrease of two SUDS points (on a scale of 1–10) from the highest to the final rating (unless when the initial SUDS rating was two or less). The final rating must have been constant or continuing to decrease over the last two ratings in the exposure.

Following each session, participants were given the study medication or placebo based on evidence that extinction learning occurred during the exposures in session, as determined through a pre-determined algorithm. At the end of each session, the fEMG assessment and BAT was conducted. Participants were given a topic to speak on, and given three minutes to prepare. Topics were standardized across participants, with the first three speeches considered to be simpler (e.g., school major talk or job talk) with the final two topics more difficult (individually chosen for each participant based on areas of difficulty, such as an embarrassing story or discussing a class topic they struggle with).
In vivo exposures were individually tailored for each participant based on an in-session assessment and discussion with the study therapist (e.g., asking individuals for directions to a specific campus location). Prior to giving the speech, the fEMG data were recorded. Trained research assistants connected participants to the fEMG recording apparatus. The fEMG apparatus measures physiological arousal and is a peripheral indicator of amygdala activation, which measures minute muscle movements of the face indicative of negative emotions. Participants were connected to the apparatus via appropriately placed electrodes and listened to a script read by a research assistant (Appendix J), which asked them to imagine giving the impromptu speech they had just prepared. Physiological measures were recorded for two minutes; at this time, participants were asked to stop imagining and continue sitting for one minute, while physiological measurements continued. After the three minutes, the participant was disconnected from the apparatus and asked to give the impromptu speech. The participant was asked to give the speech for at least 30 seconds before stopping (however, participants were free to terminate the exposure at any time, and were reminded of this prior to beginning the BAT). They were encouraged to continue the speech as long as they were able, with a maximum duration of five minutes. During the speech, participants were asked to report their SUDS ratings, which were recorded by a research assistant (Appendix F). The BATs were videotaped for data collection purposes. Videotaped speeches were viewed and rated by two trained research assistants using the TBCL.

At the completion of all 10 therapy sessions, or when criteria were met for termination (achievement of a specified maximum score on the LSAS indicating mild social anxiety symptoms consistently for two sessions), participants were asked to attend
a follow-up appointment. This occurred one month following the final treatment session and consisted of the completion of a follow-up assessment utilizing the aforementioned assessments. In addition, to provide additional data to evaluate the durability of any observed effects, participants underwent a planned six-month re-assessment following the final treatment session. After this follow-up meeting, participants were considered to have reached termination; however, if any participants expressed a desire for additional services at any point following participation, they were referred to the WMU Counseling Center or WMU Psychology Clinic.

**Participation Compensation**

Participants were eligible to receive bonus points in current psychology classes, if approved by their instructors. This is not believed to have introduced a significant confound, as participants randomized into the study were assessed for anxiety by trained assessors. In addition, the lengthy time commitment required likely overrode the effects of bonus points as the sole motivator for participation. Given the lengthy time commitment of the study and the follow-up assessments, other incentives were also available. At the completion of each session, participants put their name in for a drawing to receive a $20 gift certificate to a retail store (Target). One drawing occurred at the end of each semester. Additionally, participants who took part in a follow-up assessment (one month and/or six month) received $10 for their additional time, provided at each follow-up assessment session.

**Treatment Adherence**

In order to be certain that the delivery of the therapy adhered to the prescribed CBT and exposure protocol in terms of completing all procedural components, treatment
integrity data were collected for a random sample of sessions. Videotapes were made of the treatment fidelity sessions without the knowledge of study therapists. This was possible as the video camera was set up in a separate viewing room (not able to be seen by therapists or participants in the therapy room) and tapes were made of each BAT at every session regardless of treatment fidelity taping. Treatment fidelity was assessed for 20% of sessions, ranging among participants, therapists, and sessions 1 through 5 (as sessions 6 through 10 utilized individualized in vivo exposure exercises that often took place outside of the therapy room). Two trained research assistants completed session-specific checklists of the essential aspects of each session.

**Human Subjects Protection**

The present study was approved by two Human Subjects Institutional Review Boards (HSIRB): Western Michigan University’s and Borgess Hospital’s (Appendix K). Both addressed ethical considerations in addition to specific attention to the medication-related issues on the part of the hospital-based HSIRB. Before the medication or placebo was prescribed, all participants met individually with the study psychiatrist 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 and midway through treatment. The medication was prescribed by a licensed and board-certified psychiatrist following the medical assessment. The psychiatrist and pharmacist were not blinded for participant protection in the possible event of adverse effects.

During the screening session, all possible measures were taken to protect the safety and welfare of participants against preventable risks. Before participation, all
participants read the informed consent document and the drug information handout and were provided opportunities to ask questions prior to consent being obtained. Upon agreement to participate, two copies of the informed consent and drug information handout were signed. One was retained by the researcher and kept in the participant’s file in the laboratory in Wood Hall, and one was given to the participant for his/her records. Participants were informed of the voluntary nature of participation and that they were able to withdraw at any time without penalty or prejudice. The informed consent document included information about what to expect in therapy, what procedures were used, the time commitment involved, potential risks and benefits, possible side effects of DCS, and confidentiality information. The drug information handout included specific information on the drug and potential side effects. The informed consent document included the names and phone numbers of the principal and student investigator, as well as the phone numbers for the Chair of the Human Subjects Institutional Review Board and for the Vice President of Research. All participants received the phone number of the psychiatrist, whom they could contact at any time if they experienced any adverse effects of the medication or if they had any further questions regarding the drug. Additionally, medical staff from the Sindecuse Health Center was available if needed.

Although exclusion criteria consisted of allergies to the medication (DCS) or pregnancy/breast feeding, some mild side effects are possible with DCS. Mild side effects include headaches, drowsiness, or dizziness. Rare, but more serious side effects that could occur (and would result in discontinuation of medication and leaving the study) included confusion, irritability, depression, muscle twitches, loss of balance, and skin rash. These effects are usually seen only with long-term use of the medication and
at doses higher than that which participants were be given, and therefore should not have been a concern in the current study. Participants were assessed for any of these risk factors and completed a medical history and drug screening by the psychiatrist during the assessment session. Prior to each treatment session, participants completed a form to indicate any potential side effects experienced, any recent changes to medication, and any recent alcohol or illicit substance consumption. All new medications taken were checked by the psychiatrist prior to administration of the pill, to ensure no contraindications existed. Participants who endorsed consumption of alcohol/illicit substances were reminded of the increased risk to side effects and requested to refrain. In the event that a participant continued to report substance use prior attending sessions, he or she was removed from the study.
CHAPTER V

HYPOTHESES

Based on the preclinical research and the majority of the limited clinical research available, there is some evidence that DCS facilitates exposure therapy, potentially by increasing the speed of initial gains. This study will test the following hypotheses:

1. Significantly greater reductions in anxiety measures, as evidenced by larger slope of change over time, in the earlier stages of treatment would be evident for the DCS group.

2. fEMG data should corroborate self-report and behavioral measures of anxiety and show decreases over time.

3. Less attrition rates will be seen in the DCS group.

4. DCS participants will show greater maintenance of improvements at the follow-up sessions as compared to the placebo group.
CHAPTER VI

RESULTS

Design and Analysis Plan

The present study was a double-blind randomized controlled trial utilizing a repeated measures design. Measures included session by session ratings on the LSAS, ASI, STAI, BFNE, SPAI, TBCL, and SUDS scores, as well as fEMG (corrugator supercilii muscle) data. Principal outcome measures consisted of the LSAS, SPAI, and BFNE, as specific measures of social anxiety, and SUDS and TBCL scores as measures of in-session extinction learning. The ASI and STAI were considered secondary measures to provide potential explanatory information regarding the other measured domains of anxiety. Except where noted, all analyses were conducted using the intent-to-treat sample ($N = 16$).

The present study consisted of a sample size smaller than anticipated. Therefore as recommended by Litz and colleagues (2012), compromise and sensitivity power analyses were conducted. Given the $N$ of 16, and the number of predictors used in the model, power was less than ideal (calculated at 0.7, as opposed to a goal of 0.8 or higher); in other words, large effect sizes are needed in order to detect potential treatment effects. As the number of parameters used increased, effect sizes would need to be higher (.6 to .7 or more) to detect effects of the interaction and main effects. Some measures met these criteria, but not all. Regardless of the results of power analyses, all analyses were completed and presented, as proposed. The implications of low power will
be further discussed. At the outset of analyses, missing data were addressed by investigating data imputation methods. The last-observation-carry-forward method (LOC) was utilized in cases of participants who completed a minimal number of sessions (e.g., 2) up until session 5, the point at which termination criteria allowed for completion. In addition, missing data across all sessions were also addressed using the single imputation method that relied on the participant’s mean score for a given measure. Preliminary results were very similar in analyses with and without the second imputation method; therefore, only the LOC dataset was used for the analyses presented.

The initial proposal planned for two potential analytic methods. A mixed between-within analysis of variance (ANOVA) was proposed, as had been used in an earlier and related study, to investigate group differences and changes over time in each group. Additionally, a linear mixed model (LMM; also referred to as mixed-effects models) was selected as a good fit for the study design. Variations of this method have been used in previous DCS treatment studies (e.g., Chasson et al., 2010; Litz et al., 2012; Smits et al., 2013). The regression model was determined to be an appropriate fit for the present study, given the utilization of repeated measures across numerous time points and use of termination criteria for completion, which resulted in a different number of sessions per participant. The LMM analysis does not require independence of variables or assumption of constant variance and allows for incomplete data sets, which offers a better method for handling missing data (West, 2009). This method was employed in the Smits et al. (2013) study, which also employed early termination criteria. Finally, the LMM model allows for the evaluation of predictor variables (which in the present case included treatment group, severity level, and degree of in-session extinction learning).
The LMM model consisted of participants treated as independent cases (subject variable) and time as the repeated variable. Group, time (sessions), and group by time interactions were entered as fixed factors. Time was entered as a continuous covariate, to estimate the functional relationship of time with scores, giving time a meaningful scale. While an alternative approach would be to specify time as a repeated factor, and then estimate means for scores at each level of time (session), the former was chosen as it provided a better fit for the data and utilized significantly less parameters (as discussed in West, 2009), preferable for the present sample. The best fit for model and covariance structure (e.g., unstructured, autoregressive, compound symmetry) was determined using the $-2 \log$ likelihood ($-2LL$), Akaike’s information criterion (AIC), and Bayesian information criterion (BIC) statistics. These statistics were examined using the smaller is better criterion as well as chi-square tests to determine if the model fit improvement was significant. The model with the best fit was then selected for presentation. The maximum likelihood method (as suggested by Singer & Wilett, 2003) was used. Additional models investigated the slope of change for each group given the particular interest of potential differences in slope early in therapy, by comparing groups separately through the fifth session only (as done by Chasson et al., 2010). Secondary analyses were also conducted to examine potential moderators of initial severity (based on findings of Litz et al., 2012, and Otto et al., 2010) and amount of in-session extinction learning (as investigated by Smits et al., 2013). Moderator analyses were conducted using the potential moderator added as a fixed factor with all possible interactions included in the model, with particular attention to the time by group by moderator interactions. To supplement the outcome analyses, effect sizes were calculated and are
presented where relevant, with \( t \) scores converted to positive values when calculating effect sizes, for clarity.

In addition to group analyses, given the small sample size as well as the high variability in treatment response, treatment completers from each group were subjected to single subject analyses. Treatment completer data were inspected graphically for the primary measure to evaluate rate, magnitude, and maintenance of change. Given the presence of LSAS data at the preliminary assessment session and the initial point of exposure learning during session 2, three baseline points of measurement were available prior to the initial treatment intervention. To investigate points of change from session to session, based on the Gaynor and Harris (2008) model, the variability from one data point to the next was compared to the overall variability in the data set. LSAS scores were converted to \( Z \) scores. The \( Z \) scores were then coded as a 1 if change occurred in the direction expected and a 0 if no reliable change occurred, or occurred in the wrong direction. This resulted in a code for each participant that would allow for investigation of early treatment change followed by the initial exposure session. Additionally, given investigations that suggest that DCS effects may be mediated by the level of extinction learning that occurs in a given session (Smits et al., 2013) the amount of in-session improvement (as measured by SUDS ratings during in-vivo exposures) was recorded. An algorithm was used by study therapists to determine if a threshold degree of learning was met in order to administer the DCS or placebo pill. While all participants evidenced change at each session and were given a pill, the criteria were liberal, consisting of a decrease of two points of SUDS from the highest during the in-vivo exercise to termination of the exercise. Therefore, amount of change was divided into either a
minimal (two to three points) or maximal (four or more) category. This allowed for
determination of sessions where significant amounts of learning occurred; these time
points were bolded in the ID score, which then permitted an examination for a significant
change following that session.

Additionally, as modeled by Wald and Taylor (2007) in a single-subject treatment
analysis, percent symptom reduction was calculated for each completer on each measure
from pre- to post-treatment, and where available, pre to follow-up at one month or six
months. Given that the small amount of follow-up data did not allow for reliable
statistical analyses to be conducted, this provided one method of preliminarily examining
follow-up maintenance. The reliable change index (RCI) was also applied to determine
potential differences in amount of change as well as maintenance of improvement
following treatment completion. A final point of single-subject investigation was in
regard to participants who may have been more severe or required more sessions (slow
responders), as has been investigated in prior studies (de Kleine et al., 2012; Norberg et
al., 2011). Given that a termination criteria allowed for participants to reach treatment
completion at any point after they reached session 5, participants who completed all 10
sessions could be conceptualized as either more severe, more intractable, or slow to
respond. This allowed for an examination investigation of whether DCS was of benefit
for such participants (although admittedly very preliminary and to be interpreted with
cautions due to sample issues discussed earlier).

Altogether, these analyses were utilized to determine potential differences in
change following initiation of the treatment component, determine where and if change
occurred, investigate differences based on severity or latency to respond, as well as
investigate if the magnitude of change in in-session extinction learning, mediated the DCS effect.

**Treatment Randomization and Attrition**

As is illustrated by Figure 1, a total of 64 participants were assessed for eligibility. Of those, 24 qualified for the study based on the screening session and were randomized into the study. Reasons for ineligibility are included in Figure 1. Of the 24 randomized participants, 16 entered treatment, with 7 in the DCS group and 9 in the placebo group. Of note, initial randomization resulted in 8 participants in each group. However, due to an error in prescription filling at the pharmacy, which was discovered after the blind was lifted, one participant assigned to the DCS group erroneously received placebo. Therefore, this resulted in unbalanced group assignments. Of participants who entered treatment, 7 completed and 9 dropped out prior to session completion. A breakdown of the number of sessions completed by each participant is illustrated in Table 1. Follow-up data (1 month and/or 6 month) is available for 5 of the 7 completers, 3 in the DCS group and 2 in the placebo group. The two primary reasons cited for dropout by participants, when reachable, were lack of interest in continuing with the study due to time constraints or personal reasons and no longer being in the area during semester or summer breaks that occurred prior to treatment completion.
Figure 1. Participant flow diagram. Completer sample sizes represent participants who reached full termination criteria. DCS indicates D-cycloserine.
Table 1

Participant Session Completion and Status

<table>
<thead>
<tr>
<th>Participant</th>
<th>Group</th>
<th>Sessions Completed</th>
<th>Completer Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>Dropout</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Dropout</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5</td>
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</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
<td>Dropout</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>10</td>
<td>Completed</td>
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<tr>
<td>8</td>
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<td>8</td>
<td>Completed</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>Dropout</td>
</tr>
<tr>
<td>10</td>
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<td>1</td>
<td>Dropout</td>
</tr>
<tr>
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</tr>
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<tr>
<td>22</td>
<td>1</td>
<td>7</td>
<td>Completed</td>
</tr>
</tbody>
</table>

Sample Demographics

Table 2 displays the demographic characteristics of the sample. All were college students, with an average age of 19.81. There were no significant differences between groups on age ($p = .08$) or gender ($p = .72$). A majority of the sample was female (63%) and non-Hispanic white (63%).
Table 2

Demographic Characteristics of Sample

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Overall (N = 16)</th>
<th>Placebo (n = 9)</th>
<th>DCS (n = 7)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>.72</td>
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<tr>
<td>Female</td>
<td>10 (63%)</td>
<td>6 (67%)</td>
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</tr>
<tr>
<td>Male</td>
<td>6 (37%)</td>
<td>3 (33%)</td>
<td>3 (43%)</td>
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</tr>
<tr>
<td>Age</td>
<td>19.81 (1.91)</td>
<td>19.00 (1.12)</td>
<td>20.86 (2.27)</td>
<td>.08</td>
</tr>
<tr>
<td>Ethnicity</td>
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<td></td>
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<td>African American</td>
<td>1 (6%)</td>
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<td>1 (13%)</td>
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</tr>
<tr>
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<td>2 (25%)</td>
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<tr>
<td>Non-Hispanic white</td>
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<tr>
<td>Hispanic white</td>
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<tr>
<td>Other</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

Adverse Effects

No significant adverse effects were noted throughout the study. Two participants indicated mild symptoms, at the time of their final sessions. One participant reported experiencing dizziness following medication administration and another reported significant experiences of fatigue. Upon lifting of the blind, it was found that both of these participants were in the placebo condition. No participants indicated alcohol consumption the day of or prior to session and medication administration. One participant, who was randomized and began treatment, reported continued use of illicit substances during the pre-session screening and was removed from the study following
session 2. In line with prior DCS treatment studies, these observations suggest it continues to show evidence of being well-tolerated by participants.

**Treatment Adherence**

As mentioned, 20% of study sessions were taped, randomly selected and unknown to study therapists. These tapes were reviewed separately by two different trained observers. Regardless of treatment group, all participants received the same intervention. Both observers indicated the presence of specific required treatment components for each session as well as noted the length of exposures and presence of non-adherent treatment components (e.g., use of relaxation strategies during exposures).

In order to determine adherence with the treatment protocol, checklist compliance percentages were computed. On 100% of observed occasions, and in relevant sessions, the therapist engaged in psychoeducation, reference to the treatment model, analyzing problem/example situations in relation to the treatment model, discussion of the previous week’s homework, and coaching. On 100% of the observed occasions, the participant engaged in exposure through rehearsal of a prepared speech, and feedback/discussion of the exposure occurred. Of these exposures, 92% met the protocol for length (minimum of 15 minutes). Proscribed therapist behaviors/topics were not noted.

**Preliminary Analyses**

The initial point of dependent variable analyses consisted of independent-samples $t$ tests to assess group differences at session 1. There were no significant differences between groups on any measures (LSAS, $p = .62$; ASI, $p = .93$; STAI, $p = .65$; BFNE, $p = .37$; SPAI, $p = .62$; TBCL, $p = .40$), aside from SUDS ratings ($p = .001$). This suggests that both groups started at comparable levels of symptom severity, with the exception of
the DCS group reporting significantly higher SUDS ratings during the BAT than the placebo group at the beginning of treatment. SUDS scores at session 1 were held constant in analyses of this measure.

An additional preliminary analysis addressed the question of potential differences in drop-out rates between the DCS and placebo groups. Of the 7 participants who completed treatment, 4 were in the DCS group and 3 were in the placebo group, resulting in a dropout rate of 43% for the DCS group and 67% for the placebo group. No differences were found between treatment completers and drop-outs on age ($p = .21$), gender ($p = .85$), or LSAS scores at assessment ($p = .38$). Chi-squared analyses, using the Yates continuity correction for a $2 \times 2$ comparison indicate that there was not a significant difference between the placebo and DCS group in rates of dropout ($t = .20$, $p = .65$). Additionally, differences in response and remission rates were considered, based on LSAS scores (used in the assessment session and at each session, and a diagnostic tool with cut-offs for determining potential diagnosis). While more DCS participants were considered treatment responders (57%) and remitters (43%) as compared to the placebo group (22% and 0%, respectively), these differences were not significant based on chi-squared analyses, using the Yates continuity correction ($p = .36$ and $p = .13$, respectively).

**Primary Analyses**

Table 3 presents the means and SDs for each measure. Primary outcome measures consisted of the LSAS, SPAI, and BFNE, as specific measures of social anxiety. Behavioral, in-session measures included SUDS, TBCL, and fEMG corrugator
**Table 3**

*Means and Standard Deviations of Measures Across Sessions*

<table>
<thead>
<tr>
<th>Session</th>
<th>Pbo Mean (SD)</th>
<th>DCS Mean (SD)</th>
<th>LSAS</th>
<th>ASI</th>
<th>STAI</th>
<th>BFNE</th>
<th>SPAI</th>
<th>SUDS</th>
<th>TBCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1</td>
<td>75.00 (17.24)</td>
<td>70.14 (20.81)</td>
<td>24.78 (6.42)</td>
<td>45.20 (9.55)</td>
<td>45.89 (9.69)</td>
<td>90.33 (19.05)</td>
<td>4.73 (1.39)</td>
<td>8.29 (2.98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.22 (17.23)</td>
<td>69.14 (19.04)</td>
<td>21.56 (6.33)</td>
<td>42.33 (8.62)</td>
<td>48.43 (7.91)</td>
<td>91.11 (26.30)</td>
<td>4.33 (1.31)</td>
<td>7.41 (2.94)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.78 (19.68)</td>
<td>65.56 (15.73)</td>
<td>22.56 (9.31)</td>
<td>43.56 (10.13)</td>
<td>47.71 (8.95)</td>
<td>67.71 (27.10)</td>
<td>4.01 (1.62)</td>
<td>7.05 (0.70)</td>
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<tr>
<td></td>
<td>65.56 (14.57)</td>
<td>62.00 (14.57)</td>
<td>20.33 (8.23)</td>
<td>42.00 (12.59)</td>
<td>44.71 (8.09)</td>
<td>67.11 (27.10)</td>
<td>4.22 (1.50)</td>
<td>6.75 (1.98)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>67.00 (18.30)</td>
<td>59.00 (19.41)</td>
<td>21.78 (8.57)</td>
<td>45.89 (13.61)</td>
<td>45.86 (11.29)</td>
<td>85.44 (22.69)</td>
<td>4.18 (1.71)</td>
<td>7.43 (2.94)</td>
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</tr>
<tr>
<td></td>
<td>57.00 (15.25)</td>
<td>50.75 (15.25)</td>
<td>20.75 (8.42)</td>
<td>45.00 (14.05)</td>
<td>49.33 (16.77)</td>
<td>85.44 (22.69)</td>
<td>4.21 (1.53)</td>
<td>7.08 (2.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>67.33 (30.27)</td>
<td>57.00 (15.25)</td>
<td>22.00 (13.52)</td>
<td>49.33 (14.05)</td>
<td>49.33 (16.77)</td>
<td>85.44 (22.69)</td>
<td>4.21 (1.53)</td>
<td>7.08 (2.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50.73 (6.80)</td>
<td>46.33 (6.80)</td>
<td>18.33 (2.31)</td>
<td>48.00 (24.51)</td>
<td>48.33 (14.57)</td>
<td>85.44 (22.69)</td>
<td>4.21 (1.53)</td>
<td>7.08 (2.38)</td>
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<tr>
<td></td>
<td>89.50 (14.85)</td>
<td>40.50 (23.33)</td>
<td>21.00 (5.66)</td>
<td>51.50 (30.40)</td>
<td>57.50 (3.53)</td>
<td>85.44 (22.69)</td>
<td>4.21 (1.53)</td>
<td>7.08 (2.38)</td>
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<tr>
<td></td>
<td>88.00 (12.73)</td>
<td>47.00 (15.00)</td>
<td>20.00 (8.47)</td>
<td>59.00 (22.63)</td>
<td>55.50 (6.36)</td>
<td>85.44 (22.69)</td>
<td>4.21 (1.53)</td>
<td>7.08 (2.38)</td>
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</tr>
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<td></td>
<td>87.00 (11.31)</td>
<td>45.00 (11.00)</td>
<td>19.00 (7.07)</td>
<td>44.00 (22.63)</td>
<td>57.00 (4.24)</td>
<td>85.44 (22.69)</td>
<td>4.21 (1.53)</td>
<td>7.08 (2.38)</td>
<td></td>
</tr>
</tbody>
</table>

**Means and SDS were calculated using LOC method up to session 5 for early drop-outs. After session 5, based on measure criterion, participants were considered completers, with completers finishing anywhere between 5 to 10 sessions.**
scores. The ASI and STAI were considered secondary measures to provide information regarding other domains of anxiety. Graphs for each measure are presented in Figures 2 through 8. Of note, due to experimental error resulting in a change to threshold and undetectable signal levels, a large portion of facial EMG measurements were compromised and unable to be analyzed. This resulted in data available for only a small subset of participants whose data were collected prior to this error/malfunction. It is believed that these data are valid, given that this threshold level change occurred at a specific time point during the study, after which no data were readable. Given this, group statistical analyses were not conducted, and these data are not presented with the primary analyses; however, it is briefly investigated in the single-subject analyses.

![Figure 2](image-url)  
*Figure 2.* Mean Liebowitz Social Anxiety Scale scores between groups ($N = 16$).
Figure 3. Mean Brief Fear of Negative Evaluation scores between groups ($N = 16$).

Figure 4. Mean Social Phobia and Anxiety Inventory scores between groups at the initial and final session ($N = 16$).
Figure 5. Mean Subjective Units of Distress Scale scores between groups ($N=16$).

Figure 6. Mean Timed Behavior Checklist scores between groups ($N=16$).
Figure 7. Mean Anxiety Sensitivity Index scores between groups (N = 16).

Figure 8. Mean State Trait Anxiety Inventory (State subscale) scores between groups (N = 16).
Analyses of Variance

The initial proposal planned for two potential analytic methods. A mixed between-within analysis of variance (ANOVA) was proposed. However, given the repeated session design and study model utilizing early termination criteria, as well as dropout rates, the ANOVA is not the most appropriate method of analysis for the present study. Additionally, most repeated-measures studies violate numerous assumptions underlying ANOVA (namely, independence of scores over time). ANOVA results will be presented briefly based on the proposal plan, followed by the primary analyses using Linear Mixed Model analysis, considered to be more suitable approach for the data.

The mixed between-within subjects ANOVA was conducted to assess the impact of group condition on participants’ scores on principal and secondary measures across five time periods, consisting of sessions 1 through 5. Given early termination criteria starting at session 5, the study design resulted in “missing data” over and above what was due to dropout. On measures where assumptions of sphericity were not met, adjusted degrees of freedom and the revised results are reported. There was no significant interaction between group and time on any of the principal measures (LSAS, $F(2.18, 11) = 0.05, p = .96$; BFNE, $F(2.60, 11) = .51, p = .66$; SPAI, $F(4, 11) = 3.54, p = .08$). Similar results were found for in-session (TBCL, $F(4, 11) = 2.50, p = .17$) and secondary (ASI, $F(2.51, 11) = .17, p = .88$; STAI, $F(4, 11) = .76, p = .57$) measures. There was a substantial main effect for time, with both groups improving over sessions, on the LSAS and ASI measures ($F(2.18, 11) = 5.57, p = .01$; $F(2.51, 11) = 3.20, p = .04$), respectively, and a trend towards significance for the BFNE ($F(2.60, 11) = 2.20, p = .06$) and SPAI ($F(4, 11) = 3.82, p = .07$). No main effects for time were found for the STAI and TBCL
measures \( F(4, 11) = 1.63, p = .18; F(4, 11) = 1.62, p = .19 \), respectively. The main effect for group was not significant for any measures (LSAS, \( F(1,14) = .56, p = .47 \); BFNE, \( F(1, 14) = .01, p = .94 \); SPAI, \( F(1, 14) = .42, p = .52 \); TBCL, \( F(1, 14) = .03, p = .87 \); ASI, \( F(1, 14) = .02, p = .90 \); STAI, \( F(1, 14) = .45, p = .51 \)). These results suggest no differences in effectiveness depending on session or overall for the DCS group over the placebo group. Given the significant difference in SUDS scores at session 1, an analysis of covariance (ANCOVA) was conducted to compare changes in SUDS scores between groups across time after controlling for initial differences in scores. After adjusting for the SUDS scores at session 1, the covariate was found to be significant. There was a strong, significant relationship between the session one SUDS and SUDS scores at each session \( (p \text{ values} < .005) \), suggesting that the SUDS scores at each session are influenced by initial SUDS scores (i.e., the DCS group began with higher levels of SUDS, and although decreased as the placebo group did, the scores remained higher across all sessions).

**Linear Mixed Model Analyses**

Mixed effects regression models were conducted on all measures to determine whether group was a significant predictor of change on measures across sessions. Prior to including group as a predictor, unconditional models were fitted to determine if change did occur over time and to use as a comparison for model fit. In the unconditional model, all measures showed significant decreases over time except for the TBCL. This finding comports well with graphical analysis, which shows significant variability in scores on this measure. Given this, the TBCL was not subjected to further analyses. All other measures were then fitted to models that included group to determine if group condition
had an impact on changes across sessions. Relevant data from these models are presented in Table 4. The models for all measures improved in regards to fit, and explained additional variance, when group condition was added into the model. However, following chi-square analyses, only the LSAS and SUDS measures improved to a significant degree ($p = .03, p = .05$) respectively. The effects of models with the addition of group will be discussed for all measures, given improvement to model as well as increased variance explained by the addition of the group factor.

With group included in the model, the primary measure of social anxiety, LSAS, evidenced a decrease in scores over time ($F(1, 10.71) = 13.21, p = .004$). However, there was a significant interaction between time and group, ($F(1, 10.71) = 6.17, p = .03$). More specifically, the placebo group showed an unsteady rate of change, with a positive slope at times ($\beta = 3.96, t(10.71) = 2.48, p = .03$). Given the significant difference between groups in SUDS scores at the time of session one, a model for SUDS data was fitted with session one SUDS scores held as a covariate. The addition of this covariate significantly improved model fit (chi-square, $p < .001$). While there was still a significant effect between groups ($F(1, 22.083) = 5.17, p = .03$) and SUDS scores at session one were a significant predictor ($F(40.65) = 17.47, p < .001$), a significant interaction effect was also present ($F(1, 20.14) = 4.71, p = .04$). This effect existed for the placebo group, which evidenced a greater decrease in slope at some point in time ($\beta = -1.00, t(22.84) = -2.17, p = .04, d = 0.9$). Other specific measures of social anxiety, BFNE and SPAI, showed a significant effect for time ($F(1, 24.93) = 7.91, p = .01; F(1, 11.12) = 8.18, p = .02$) but not an interaction effect ($F(1, 24.91) = 3.36, p = .09; F(1, 11.19) = 4.07, p = .07$) although there was some evidence of a trend toward significance. There were no interaction
Table 4

**Linear Mixed Model Effects of Time and Group by Time for Primary and Secondary Outcome Measures Across Sessions**

<table>
<thead>
<tr>
<th>Model with group</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LSAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>-4.87</td>
<td>-4.33</td>
<td>.001</td>
<td>2.58</td>
</tr>
<tr>
<td>Time × group</td>
<td>3.96</td>
<td>2.48</td>
<td>.03</td>
<td>1.51</td>
</tr>
<tr>
<td><strong>SUDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>-0.54</td>
<td>-1.90</td>
<td>.30</td>
<td>0.34</td>
</tr>
<tr>
<td>Group</td>
<td>7.30</td>
<td>2.27</td>
<td>.03</td>
<td>0.97</td>
</tr>
<tr>
<td>Time × group</td>
<td>0.34</td>
<td>1.35</td>
<td>.19</td>
<td>0.42</td>
</tr>
<tr>
<td>Session 1 SUDS cov</td>
<td>1.90</td>
<td>3.81</td>
<td>.01</td>
<td>1.40</td>
</tr>
<tr>
<td>Session 1 SUDS × group</td>
<td>-1.00</td>
<td>-2.70</td>
<td>.04</td>
<td>0.90</td>
</tr>
<tr>
<td>Session 1 SUDS × time</td>
<td>0.002</td>
<td>0.03</td>
<td>.97</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>BFNE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>-0.50</td>
<td>-4.96</td>
<td>&lt;.001</td>
<td>2.07</td>
</tr>
<tr>
<td>Time × group</td>
<td>0.33</td>
<td>2.40</td>
<td>.03</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>SPAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>-14.17</td>
<td>-3.14</td>
<td>.01</td>
<td>1.88</td>
</tr>
<tr>
<td>Time × group</td>
<td>11.72</td>
<td>2.02</td>
<td>.07</td>
<td>1.21</td>
</tr>
<tr>
<td><strong>ASI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>-1.51</td>
<td>-3.5</td>
<td>.004</td>
<td>1.92</td>
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<td>Time × group</td>
<td>0.14</td>
<td>0.24</td>
<td>.82</td>
<td>0.13</td>
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<td><strong>STAI</strong></td>
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<tr>
<td>Time</td>
<td>-1.59</td>
<td>-2.51</td>
<td>.02</td>
<td>0.86</td>
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<td>Time × group</td>
<td>1.17</td>
<td>1.38</td>
<td>.18</td>
<td>0.48</td>
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<table>
<thead>
<tr>
<th>Model with predictors</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>d</th>
</tr>
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<tbody>
<tr>
<td><strong>LSAS</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Severity score</td>
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<td>2.925</td>
<td>.01</td>
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<tr>
<td>Group × time</td>
<td>-11.85</td>
<td>-2.12</td>
<td>.05</td>
<td>1.11</td>
</tr>
<tr>
<td>Group × time × severity</td>
<td>0.33</td>
<td>2.96</td>
<td>.01</td>
<td>1.67</td>
</tr>
<tr>
<td><strong>SPAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score</td>
<td>1.32</td>
<td>2.20</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Group × time</td>
<td>-46.05</td>
<td>-1.81</td>
<td>.10</td>
<td>1.07</td>
</tr>
<tr>
<td>Group × time × severity</td>
<td>0.56</td>
<td>2.33</td>
<td>.04</td>
<td>1.38</td>
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<tr>
<td><strong>BFNE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score</td>
<td>0.42</td>
<td>1.49</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Group × time</td>
<td>-6.65</td>
<td>-3.57</td>
<td>.002</td>
<td>1.49</td>
</tr>
<tr>
<td>Group × time × severity</td>
<td>0.16</td>
<td>4.18</td>
<td>&lt;.01</td>
<td>1.83</td>
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<tr>
<td><strong>SUDS</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score</td>
<td>-0.004</td>
<td>-0.07</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>Group × time</td>
<td>1.16</td>
<td>2.10</td>
<td>.05</td>
<td>0.81</td>
</tr>
<tr>
<td>Severity × time</td>
<td>0.02</td>
<td>2.72</td>
<td>.01</td>
<td>1.05</td>
</tr>
<tr>
<td>Group × time × severity</td>
<td>-0.01</td>
<td>-1.28</td>
<td>.21</td>
<td>0.49</td>
</tr>
</tbody>
</table>
effects for either of the secondary measures, ASI and STAI, ($F(1, 13.17) = .06, p = .82$; $F(1, 33.92) = 1.91, p = .18$) but there was a main effect of time ($F(1, 13.17) = 22.42, p < .001; F(1, 33.92) = 5.65, p = .02$).

**Slope of Change Throughout Treatment**

One area of interest for the present study included the general difference in slopes, and particularly the potential for differences in slopes earlier in therapy, based on prior studies (Chasson et al., 2010). Therefore, change over time was analyzed for each group separately, overall and in the first half of treatment (sessions 1 through 5), with results further detailed in Table 5. In general, early change in scores was not robust in the present study, although when evident, was in favor of the DCS group. On a majority of measures, no significant slopes of change were found early in treatment. However, significant decreases in scores in the first five sessions were found for the DCS group on the LSAS ($\beta = -2.80, t(11.15) = -2.64, p = .02$) and SUDS ($\beta = -.79, t(7.34) = -3.70, p = .01$) scores. Effect sizes were large and robust for both LSAS ($d = 1.5$) SUDS ($d = 2.73$).

Slopes of change over the full course of sessions were variable. Benefits were evident for the DCS group over placebo in slope of change over time across all sessions. The DCS group showed favorable improvements over the placebo group for the LSAS ($\beta = -4.23, t(44.94) = -4.00, p < .001$ vs. $\beta = -1.15, t(6.65) = -1.19, p = .28$) and the ASI ($\beta = -1.12, t(28.60) = -2.11, p = .04$ vs. $\beta = -1.12, t(22.41) = -1.84, p = .07$). Large effect sizes were seen for both measures for the DCS group ($d = 1.19$ and $d = .78$). Similar to earlier findings, the STAI showed no significant decrease for the DCS group ($\beta = -1.31, t(15.58) = -1.44, p = .17$); the placebo group showed an increase overall,
Table 5

*Slope of Change Scores Comparing the First Half of Sessions to the Full Course of Sessions Between Groups*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Measure</th>
<th>First Half Slopes</th>
<th>Full Slopes</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>$\beta$</td>
<td>$t$</td>
</tr>
<tr>
<td>LSAS</td>
<td>DCS</td>
<td>-2.80</td>
<td>-2.64</td>
</tr>
<tr>
<td></td>
<td>Pbo</td>
<td>-1.4</td>
<td>-1.66</td>
</tr>
<tr>
<td>BFNE</td>
<td>DCS</td>
<td>-1.04</td>
<td>-1.44</td>
</tr>
<tr>
<td></td>
<td>Pbo</td>
<td>-0.29</td>
<td>-0.88</td>
</tr>
<tr>
<td>SPAI</td>
<td>DCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pbo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUDS</td>
<td>DCS</td>
<td>-0.79</td>
<td>-3.7</td>
</tr>
<tr>
<td></td>
<td>Pbo</td>
<td>-0.7</td>
<td>-1.87</td>
</tr>
<tr>
<td>ASI</td>
<td>DCS</td>
<td>-1.28</td>
<td>-1.61</td>
</tr>
<tr>
<td></td>
<td>Pbo</td>
<td>-0.98</td>
<td>-1.95</td>
</tr>
<tr>
<td>STAI</td>
<td>DCS</td>
<td>-1.49</td>
<td>-1.58</td>
</tr>
<tr>
<td></td>
<td>Pbo</td>
<td>.006</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Note.* The SPAI was only administered at the beginning and end of treatment; therefore, no first half data is available.

* indicates significant change.

although not a significant one ($\beta = .36$, $t(18.49) = .36$, $p = .72$). The BFNE, while evidencing a decreasing trend, was not significant for either group (DCS, $\beta = -1.2$, $t(7.47) = -2.06$, $p = .08$; placebo, $\beta = -1.1$, $t(33.19) = -.17$, $p = .87$) with a similar pattern seen for the SPAI (DCS, $\beta = -17.6$, $t(2.93) = -2.52$, $p = .09$; placebo, $\beta = -2.3$, $t(6.53) = -.86$, $p = .42$). Both groups showed significant decreases in SUDS scores over
time (DCS, $\beta = -.50$, $t(11.40) = -3.52$, $p = .005$; placebo, $\beta = -.19$, $t(1, 11.89) = -3.88$, $p = .002$), both with large effect sizes ($d = 2.08$, $d = 2.25$, respectively).

**Potential Predictors/Moderators Analyses**

Following the primary model of interest with addition of group as a factor, and evidence based on Wald Z significance levels, indicating that much variance was left to be explained, other potential predictors were included in model analyses. These potential predictors included initial severity level (as measured at the screening assessment session, with a higher Anxiety Disorder Inventory Schedule (ADIS) component score indicating higher severity) and amount of extinction learning that occurred in session. Initial severity scores were added into the models as a covariate. With the addition of this predictor, the model fit improved to a significant degree for the LSAS (chi-squared, $p = .01$), BFNE ($p = .01$), SPAI ($p = .04$), and SUDS ($p = .03$). While the $-2\log$ likelihood scores improved for the ASI and STAI, it was not a significant improvement ($p = .26$, $p = .09$, respectively).

For the LSAS, with both group condition and initial severity considered as predictors, the group by time interaction remained significant ($F(1, 14.52) = 4.49$, $p = .05$) and severity level was a significant predictor ($F(1, 21.45) = 6.91$, $p = .02$). Additionally, the interaction between group, time, and severity level was significant over and above these other effects ($F(1, 14.50) = 2.22$, $p = .04$). Specifically, when the initial severity level was higher, the placebo group, as compared to the DCS group, did not decrease as steadily, and in fact, showed an increase in scores at some point in time ($\beta = .33$, $t(14.50) = 2.96$, $p = .01$). Similar results were found for the SPAI, where an interaction effect between group, time, and severity level was significant ($F(1, 11.38) = $
5.45, \( p = .04 \)); when initial scores were high, the placebo group evidenced an increase in slope (lack of improvement) over time (\( \beta = .56, t(11.38) = 2.33, p = .04 \)), as compared to the DCS group. Additionally, the severity score itself remained a significant predictor (\( F(1, 30.16) = 7.12, p = .01 \)) as did an interaction between initial severity level and time (\( F(1, 11.38) = 5.45, p = .04 \)). For the BFNE, the combination of group, time, and initial severity level was significant (\( F(1, 20.84) = 17.48, p < .001 \)), showing a similar pattern as with other measures; when severity level was high, the placebo group performed more poorly (\( \beta = .16, t(20.87) = 4.18, p < .01 \)). The group by time interaction remained significant (\( F(1, 23.07) = 12.72, p = .002 \)). When initial severity level was added to SUDS data, the time by severity level interaction (\( F(1, 24.71) = 6.33, p = .02 \)) remained significant, where those with greater initial severity levels showed less improvement on SUDS as compared to other participants regardless of group condition (\( \beta = .02, t(26.65) = 2.72, p = .01 \)).

A secondary process analysis consisted of evaluating the potential predictor of in-session extinction learning that occurred and its effect on session change. While all participants evidenced some in-session change (as judged by decrease in SUDS scores during the in vivo exercise) the amount of change varied. Change scores were coded for small or marked amount of change on in-session SUDS scores, representing a continuous covariate at each session. When in-session change scores were added to the models for each measure, all model fits improved, with significant chi-square tests (all \( p < .001 \)). However, no significant interaction effects were seen with the in-session learning that occurred for any measures. These results should be interpreted with caution, given that
scores were needed at each session, resulting in a smaller usable sample with relevant data.

**Single Subject Analyses**

As discussed previously, data for all completers were investigated in greater detail. The first point of analysis for single-subject information investigated percent reduction in scores from pre- to post-treatment, and where available, pre to follow-up (one month or six month) as well as reliable change criterion, to examine overall differences in amount of change as well as maintenance of improvement following treatment completion. This information is presented in Table 6. As discussed previously, 3 out of 4 DCS participants evidenced reliable change on a majority of measures, whereas only 1 of 3 placebo participants showed reliable improvement over time. Based on the LSAS cut-off scores, by the final session, 2 of 4 DCS participants no longer met criteria for social anxiety and the other 2 fell within the minimal symptom category. Of these 2, 1 participant no longer met criteria for social anxiety by the one-month follow-up. All 3 placebo participants still met criteria for social anxiety—2 within the minimal symptom category and 1 remaining in the severe category—with no continued improvements noted at follow-up for those with data available.

The individual graphs for the LSAS are presented in Figures 9 and 10. Based on hypotheses, decreases were expected to begin to be evident between session two and three, and a greater slope of change earlier on would be expected for the DCS group over the placebo group. Based on visual analysis and Z score changes for individual participants, presented in Table 7, while change generally began occurring at the
Table 6

Percent Change and Reliable Change on Outcome Measures for Treatment Completers

<table>
<thead>
<tr>
<th>Participant</th>
<th>Measure</th>
<th>% reduction from pre to final</th>
<th>% reduction from pre to 1 month</th>
<th>% reduction from pre to 6 month</th>
<th>Reliable change criterion met</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3</td>
<td>LSAS</td>
<td>65</td>
<td>-</td>
<td>56</td>
<td>Yes</td>
</tr>
<tr>
<td>DCS gp</td>
<td>ASI</td>
<td>38</td>
<td>-</td>
<td>40</td>
<td>Yes</td>
</tr>
<tr>
<td>*5 sessions</td>
<td>STAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>32</td>
<td>-</td>
<td>25</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>34</td>
<td>-</td>
<td>66</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>89</td>
<td>-</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P7</td>
<td>LSAS</td>
<td>53</td>
<td>47</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>DCS gp</td>
<td>ASI</td>
<td>75</td>
<td>75</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>*10 sessions</td>
<td>STAI</td>
<td>35</td>
<td>59</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>38</td>
<td>54</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>44</td>
<td>83</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
<td>25</td>
<td>58</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P8</td>
<td>LSAS</td>
<td>75</td>
<td>75</td>
<td>83</td>
<td>Yes</td>
</tr>
<tr>
<td>DCS gp</td>
<td>ASI</td>
<td>11</td>
<td>11</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>*8 sessions</td>
<td>STAI</td>
<td>26</td>
<td>26</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>30</td>
<td>30</td>
<td>18</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>36</td>
<td>57</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
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<td>32</td>
<td>-</td>
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<td>Yes</td>
</tr>
<tr>
<td>DCS gp</td>
<td>ASI</td>
<td>62 (increase)</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>*7 sessions</td>
<td>STAI</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>7 (increase)</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>86</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P17</td>
<td>LSAS</td>
<td>3 (increase)</td>
<td>10</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td>Pbo gp</td>
<td>ASI</td>
<td>33</td>
<td>67</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>*10 sessions</td>
<td>STAI</td>
<td>9</td>
<td>22</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
initiation of treatment, notable change, when it occurred, began a bit later than expected (i.e., at session 4 or 5). While not as early as expected, some change is observable in the first half, by session 5. Visual inspection of the single-subject data is generally in line with the LMM model analyses. There does not appear to be notable difference in changes between groups, aside from some indication that DCS participants may have evidenced more continuous, or stable, change over time. And while a limited amount of follow-up data was available, DCS participants showed continued improvements at follow-up, whereas placebo participants did not. In looking at significant in-session learning as a potential predictor for improvement following the next session, which would be indicated by a change (noted with a 1) following a bolded number code. The amount of learning that occurred in a given session did not appear to significantly predict improvement at the next session for most participants. In other words, in-session

<table>
<thead>
<tr>
<th>Participant</th>
<th>Measure</th>
<th>% reduction from pre to final</th>
<th>% reduction from pre to 1 month</th>
<th>% reduction from pre to 6 month</th>
<th>Reliable change criterion met</th>
</tr>
</thead>
<tbody>
<tr>
<td>P19 Pbo gp *7 sessions</td>
<td>LSAS</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
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<tr>
<td></td>
<td>ASI</td>
<td>62 (increase)</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>STAI</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>7 (increase)</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>86</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P22 Pbo gp *7 sessions</td>
<td>LSAS</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
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<td></td>
<td>ASI</td>
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<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>STAI</td>
<td>18 (increase)</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>BFNE</td>
<td>36</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>SPAI</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SUDS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>TBCL</td>
<td>70</td>
<td>-</td>
<td>-</td>
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</table>
Figure 9. Single subject graphs for the primary measure, Liebowitz Social Anxiety Scale–DCS group. Dotted horizontal line indicates the cut-off point of diagnostic criteria for symptoms. The star indicates the first point of within-subject reliable change.
Figure 10. Single subject graphs for the primary measure, Leibowitz Social Anxiety Scale–Placebo group. Dotted horizontal line indicates the cut-off point of diagnostic criteria for symptoms. The star indicates the first point of within-subject reliable change.
Table 7

_Identity Codes for Single Subject Analyses for the Leibowitz Social Anxiety Scale_

<table>
<thead>
<tr>
<th>ID Code</th>
<th>Group</th>
<th>ID Code</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>000-111-1</td>
<td>Participant 3</td>
<td>000-111-1</td>
<td>Participant 17</td>
</tr>
<tr>
<td>000-01011111-1</td>
<td>Participant 7</td>
<td>000-111-1</td>
<td>Participant 19</td>
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<tr>
<td>000-000111-11</td>
<td>Participant 8</td>
<td>000-111-1</td>
<td>Participant 22</td>
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<tr>
<td>001-00011</td>
<td>Participant 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* 0 indicates no change and 1 indicates significant change in the direction of improvements. Bolded numbers indicate sessions where significant learning occurred during in-session exposure.

exposures resulting in significant extinction learning were not followed by notable decreases in symptoms the following session.

An additional in-session process measure included the facial EMG measures. As mentioned earlier, while equipment errors prevented statistical analyses of this measure, for participants where multiple session points were usable, data was plotted and compared to SUDS ratings for the BAT at the end of each session using visual inspection. Given the different scales for both measures, they were converted to standardized scores in order for visual comparison. As can be seen in Figure 11, the facial EMG measures did not align at each session significantly with SUDS ratings. However, decreases were seen in general, indicating a decrease in negative affect during the visual imaging of a speech situation.

As discussed previously, participants who completed all 10 sessions could be considered more severe or to be late responders. In the present study, 3 participants fit this category, 1 in the DCS group and 2 in the placebo group. At the end of 10 sessions,
the DCS participant showed reliable change on all measures, with continued decrease/improvement at one month follow-up. By contrast, both placebo participants did not evidence reliable change on most measures, and showed increases in scores on some measures. Additionally, both participants maintained similar same levels at one-month follow-up.
Figure 11. Standard scores for fEMG measures over time and as compared to SUDS during the BAT for participants where available.
CHAPTER VII
DISCUSSION

The purpose of the present study was to further investigate domains of increasing interest in the area of DCS facilitation, namely, slope of change across time and boundary conditions, or moderators, of DCS effects. It sought to better determine if DCS improves exposure-based therapy in the population of interest, by how much, and under what conditions. This was addressed by utilizing repeated measures, including potential predictors, to investigate more specific effects. The present work aimed to test the following hypotheses:

1. Significantly greater reductions in anxiety measures, as evidenced by larger slope of change over time, in the earlier stages of treatment would be evident for the DCS group.
2. fEMG data should corroborate self-report and behavioral measures of anxiety and show decreases over time.
3. Less attrition rates will be seen in the DCS group.
4. DCS participants will show greater maintenance of improvements at the follow-up sessions as compared to the placebo group.

Based on emerging evidence within the field, secondary investigations evaluated the potential moderator effects of initial severity, in-session learning, and late-responder status. Discussion of results will be primarily based on the LMM, as opposed to the
ANOVA, analyses, per earlier discussion of the better analytic method for the study design and resulting data.

The first hypothesis was partially supported, in that while change was not generally apparent in the earlier stages of treatment, over the full course of sessions, some measures evidenced differential effects depending on group assignment. More specifically, when examining slope of change during the first few sessions, the only significant change was on LSAS and SUDS scores for participants receiving DCS. This improvement generally held when looking at slope of change across all sessions for the LSAS. Additionally, the DCS group showed a significant improvement in ASI scores over time, and both groups evidenced significant change in SUDS scores over time. These results suggest that while the differences were not robust, participants who received DCS appeared to benefit to a somewhat greater extent than those who received placebo. While this benefit did not notably occur early in treatment, it became more apparent over the full course of sessions. In looking at the full models with interactions included, an interaction effect occurred for the primary measure (LSAS), with the DCS group evidencing a more stable slope of change. The other measures of social anxiety, BFNE and SPAI, evidenced a significant effect for time in the full model, but only a trend towards a significant interaction. With these measures the DCS group again showed more stable changes over time. Measures of in-the-moment anxiety and general anxiety sensitivity, STAI and ASI, showed no interaction effects.

Overall, results support the conclusion that DCS does facilitate additional treatment improvement, although this enhancement is not robust or consistent across multiple indices. See below for a brief discussion of power limitations of the present
investigation and a careful examination of obtained effect sizes in the present study. While the present findings are in contrast to earlier investigations of DCS effects with a social anxiety population (e.g., Hofmann et al., 2006), this is in line with more recent investigations with other anxiety disorder populations and a growing body of DCS treatment research. This work shows a more variable picture of facilitation effects (de Kleine et al., 2012; Litz et al., 2012; Smits et al., 2013).

As discussed earlier, given the small sample size, power analyses indicated that large effect sizes would be required in order to evidence significant changes. Generally speaking, large effect sizes were seen among both groups on numerous measures, indicating that power was likely sufficient to detect significant change when it existed. However, there were occasions where non-significant results evidenced large effect sizes, which may indicate that sample size hindered the examination of potential differences, or that although change was substantial, it was not to a level of statistical significance. For example, in looking at the slope of change for participants receiving DCS over the first half of sessions and the full course, large effect sizes were seen, indicating that substantial decreases in scores occurred, that did not reach significance. To illustrate, both the BFNE and SPAI evidenced large effect sizes for the DCS group over the full course of treatment that was not evident in the placebo group, but were not accompanied by significant change scores. Overall, the DCS group generally evidenced greater effect sizes as compared to the placebo group.

Considering initial severity as a potential moderator of effects appeared to be useful in explaining additional variance. For participants with higher severity, as judged by greater initial ADIS scores, DCS appeared to provide additional benefit. This aligns
with other DCS research in panic disorder and PTSD populations (de Kleine et al., 2012; Otto et al., 2010) and has been discussed in the literature. While DCS may not provide significant incremental value in facilitating improvements for participants as a whole, it may be beneficial for use with more severe populations, or those who are slow to respond. In light of recent findings with PTSD populations, other investigators have discussed the need for “careful attention to clinical moderators over a one-size-fits-all approach to the use of cognitive enhancers” (Litz et al., 2012). Those who may fail to respond to exposure based therapy alone, or be slow to respond, may particularly benefit from the use of cognitive enhancers, as discussed by de Kleine and colleagues (2012). The present study did not yield enough participants with either early or late completer status to allow for statistical analysis of pertinent data in the present investigation. However, the single-subject data in the present study fit with what would be expected if that trend were to hold true, in that of the participants who required all 10 sessions (i.e., did not reach termination criteria), only the participant receiving DCS evidenced improvement at the end of those 10 sessions.

Related to the discussion of symptom severity and late-response status, investigators have specifically addressed the use of DCS for treatment non-responders in an OCD population (Norberg et al., 2011), with preliminary evidence for DCS benefits for this population. The two participants in the present study who received placebo and did not evidence notable improvement over all 10 sessions could be conceptualized as treatment non-responders. It would be interesting to speculate about potential benefits of a second round of therapy with DCS facilitation. While the present findings cannot reach
any conclusions on this matter, the data do support other investigators’ conclusions that this may indeed be a fruitful area of future research.

As discussed, due to experimental error, fEMG data were unfortunately not analyzed and compared between groups. For participants where full data were available, these scores were considered within the single-subject analyses. In general, the level of corrugator activity, an indicator of negatively-valenced emotion, decreased across sessions during a task requiring participants to create an imaginal speech scenario. The slight indication of a decrease in this physiological measure of anxiety supports its use in future investigations to aid in our understanding of changes in anxiety experiences over time, and may aid in interpreting future results. Despite general decreases overall, the fEMG scores did not map on to the SUDS scores during the BAT to a notable degree. It is, however, not known how similarly physiological data would mirror self-report scores, and an immediate parallel is not necessarily expected. It is not unequivocally known how physiological symptoms and self-report ratings of anxiety map on to one another. It may be that prior to an individual becoming aware of improvement, he/she experiences a decrease in physiological arousal in response to a stressor or anxiety trigger, or alternatively, physiological arousal changes follows noted improvements in anxiety as measured by self-reporting. Time will better tell the usefulness of physiological data on our understanding of improvements in anxiety disorders. Additionally, decreases in symptomatology and physiological arousal (such as corrugator activity or skin conductance) are not the sole objective of therapy. The overarching goal is increased flexibility (behavioral and cognitive) and improved quality of life, that may or may not occur in conjunction with decreases in physiological reactivity to anxiety triggers.
In regard to the third hypothesis, investigating attrition rates, the DCS group evidenced less dropout as compared to the placebo group (43% vs. 67%), but this difference was not statistically significant. It cannot be determined at this time whether this lack of significance is due to small sample size or is evidence of a lack of benefit in this area for DCS. Additionally, the dropout rate overall was quite high in this study, likely for numerous reasons, related and unrelated to the questions of interest in the present study. Other investigators (see de Klein et al., 2012) reported dropout rates that, while lower than in the present study, also did not differ significantly between groups. Therefore, while DCS facilitation may result in treatment benefits in regard to improvement of symptoms over time, this may not support lower rates of treatment attrition as had been hypothesized, although further investigation into this question is warranted. Additionally, in looking at overall treatment response/remission, while more participants who received DCS evidenced improvement, and were also categorized as remitted as compared to the control group, this difference was also not statistically significant. It is difficult to determine based on the available data if this indicates a lack of significant facilitation overall for DCS or is a function of the high dropout rates resulting in a small sample of completers, where we would expect to see more treatment improvement.

The fourth hypothesis sought to investigate the maintenance of treatment gains at follow-up. Given the small number of participants who returned for follow-up assessments, strong conclusions cannot be made at this time. With the available data, those receiving DCS evidenced maintenance of improvements, and at times, further improvement that was not evident in the control group. While prior research in this area
generally reported minimal follow-up data, when this was investigated (see Litz et al., 2012), six-month follow-up data were not significant for time or interaction. Given the clinical importance of maintenance of treatment gains, it is worthwhile to further investigate this in future DCS studies. Preclinical evidence supports the notion that this a potential benefit of DCS adjunct use.

Two additional points based on present findings are worth a brief discussion. First, while there was evidence for differential improvements with social-anxiety specific measures (e.g., LSAS), measures of state anxiety and anxiety sensitivity did not show a similar pattern. Although they decreased generally over time, these changes were variable across sessions and between groups. Given the focus of exposure-based CBT sessions, one would not necessarily expect to see changes on anxiety sensitivity, and while changes in this experience may serve as a mediator of treatment effects for anxiety disorders, is not necessary for improvement. It is interesting that changes in state measures of anxiety were not evident, in that one would expect successful safety learning to be evident during in-the-moment anxiety experiences. This measure, however, was not administered during exposures themselves (as SUDS scores were, and did evidence improvement over time). Nonetheless, it is still interesting that these measures did not align as hypothesized and is interesting in regard to considering the type of safety learning that occurs and where and when that is evident.

A final, and important, point of discussion lies in the in-session learning, and more specifically, the administration of DCS following sessions as opposed to prior to sessions. While early preclinical literature administered DCS both before and immediately after session, clinical trials have almost exclusively administered DCS prior
to session. Some theorists noted the possible benefits of administration following session, given the potential for inadvertently facilitating increased fear learning if unsuccessful exposures occurred. Interestingly, one group of investigators reported such an occurrence (Smits et al., 2013). As discussed in the literature review, their study administered DCS following sessions of in vivo exposure for height phobia. Not only did DCS not show benefits over placebo, but those who received DCS performed more poorly, resulting in worsening of symptoms at the end of treatment. Notably, these researchers had not used in-session SUDS ratings to determine whether to administer the medication. The data were re-analyzed, separating out participants who had and had not evidenced learning in session, based on SUDS scores during virtual reality exposure. When this was done, DCS resulted in significant improvements for those who showed an in-session response and significant worsening of symptoms when in-session learning did not occur, essentially strengthening the fear learning. In the present study, DCS was administered following session, but only based on SUDS decreases in session. However, the algorithm chosen was not previously tested in empirical research, but required a decrease of 2 SUDS points (on a 0–10 scale), and all participants met this criterion. So while participants did not evidence worsening of fear in session that would have had the potential to be strengthened by DCS, the “amount” of learning may not have been sufficient. In other words, it may be that the amount of extinction learning was not sufficient to yield potential benefits. While the present study standardized the length of in vivo exposures, they were not notably long, and potentially not sufficient enough for substantial extinction learning. In the present investigation, the SUDS changes in session were re-coded, with four or more points considered a large change and three or less
considered a small change (in a method modeled off of the work by Smits et al., 2013). Given that individual participants evidenced varying amounts of SUDS changes at each session, change scores were entered as a continuous covariate at each session. When this was added as a potential predictor, no effects were seen. However, given the small amount of usable data and the continuous nature of this variable, it is possible that the power was too small to detect a difference. Single-subject examination of this area also did not suggest this pattern. Of note, it is not unequivocally known when one would expect the change in scores following a successful and meaningful in-session exposure, and the out-of session self-exposures may be a relevant confound in this regard, as it is not known how this may have affected outcome at each following session. Regardless of present findings, this is an area of potentially fruitful research, and an important one to consider for clinical use of this adjunct. This would also make use of information that has been gleaned from preclinical work.

**Strengths**

The present study built upon prior work by utilizing more stringent inclusion criteria in regard to social anxiety symptoms and providing a fuller “dose” of therapy. It also further systematized the in-vivo doses of exposures, resulting in more similarity among participants, reducing this as a potential confound. A primary strength of the present study is in the generally successful use of DCS administration immediately following session. This represents, to this writer’s knowledge, the first use of post-session administration of DCS, as suggested by preclinical evidence with no detrimental effects. This was also done following careful consideration of in-session exposure/safety learning. Such findings further support the belief that DCS influences the reconsolidation
of extinction/safety learning that occurs for hours following a successful exposure session. This application of DCS adjunct use is also more relevant to clinical application.

**Limitations**

The current study also has notable limitations. First, the sample size was smaller than had been anticipated, potentially affecting the power needed to best analyze some of the research questions (such as dropout or remission rate, effects of in-session learning, etc.). Given a lack of response by study completers, the follow-up data were not received for most participants as had been intended, preventing some conclusions on questions of DCS facilitation of exposure therapy. An additional, notable limitation lies in the lack of fEMG data as a result of experimental error. This had been part of initial study hypotheses and was not able to be investigated as planned due to a systematic breakdown in equipment functioning that went undetected contemporaneous with data collection. The limited data that were reported were all validly collected prior to this equipment malfunction. Despite the limits of physiological data discussed earlier, further use of these measures may better determine their usefulness and/or validity as a dependent variable when investigating improvements in anxiety.

In regard to dose considerations, while the in-session exposure had been systematized, the protocol also utilized assignment of out-of-session session exposures, to further individualize the treatment targets and used during in-session cognitive approaches. While this approach has been used in DCS studies (de Klein et al., 2012), others have explicitly not used this method (Litz et al., 2012), with the authors noting that this outside exposure would occur for both groups without the combination of DCS, which would confound the results. The present study did not specifically track amount of
out-of-session self-exposures conducted, so there is no way to know if participants engaged in this practice and how this may have impacted results.

Finally, and important to consider for both theoretical and clinical implications, participants who engaged in multiple sessions of the full protocol received numerous DCS pills, up to nine if they completed all sessions. While this administration is still acute, questions have been raised in the literature about how many doses of DCS should be administered for the most beneficial effect. While this information has not been determined, it has been argued that several doses may create insensitivity to its effects and may hinder potential benefits (Parnas et al., 2005). It has been suggested that regardless of the number of sessions, only a couple of administrations of DCS should be given in the initial stages of treatment given preclinical findings that DCS is more effective when given in a limited number of times (Kaplan & Moore, 2011; Vervliet, 2008). Systematic research, in both preclinical and clinical work, would be beneficial to further elucidate these parameters, and is important to determine prior to use in clinical settings.

Conclusions and Recommendations for Future Research

The present study provides some evidence of facilitory effects of DCS, but to a limited degree, with no incremental benefit noted in many cases. It does offer additional, although preliminary, information on potential moderators and particular subpopulations that may benefit the most from this adjunct use. As the literature base has grown in this area, some of the initial strong findings have given way to less robust effects, although benefits continue to be evident. What has increased, importantly, is information on the limits and potential moderators of DCS effects.
Initial severity level has emerged as an important moderator as well as the potential for benefits with a subset of late-responders and treatment non-responders. This relates directly to the evidence that DCS has been shown to activate previously “silent” synapses (Bermudo-Soriano et al., 2012) and its proposed dual action of facilitation which affects both receptor potentiation of some synapses and the depotentiation of others, potentially preventing fear reinstatement (Krystal, 2012). Additionally, as mentioned earlier, the number of DCS doses used within treatment needs to be explicitly examined, as continued administration may be redundant at the least, and prevent future learning benefits at worst. In regard to dosing, there is some evidence that DCS seems to lose its effects with repeated and pre-extinction use (Parnas et al., 2005). Another worthwhile area for future research lies in more objective measures; recent research published in the last one to two years has continued to utilize only self-report data. While this can be argued to be the most relevant for clinical population, objective and physiological data would further support such self-report data and may evidence change that is not seen in self-report measures, potentially providing useful information. While the present study was unable to analyze such physiological measures as initially planned, this is an area of potentially fruitful future research. An additional, and important area worth further investigation, lies with administration post-session and specifically following successful exposure. How best to determine that remains to be seen, but should be realized through further investigation. This would represent an important example of the translational nature of this work, to the benefit of clinical patients and further understanding of the extinction learning/reconsolidation nature of exposure therapy and the effects of NMDA facilitators.
Finally, in looking at the translation of preclinical work to clinical populations, a valuable point of future investigations (from a conceptual and methodological perspective) would be in the consideration of the validity of basic fear conditioning and extinction as a model for clinical anxiety disorders, and in this particular case, social anxiety disorder. It may be useful to investigate other types of fear conditioning stimuli aside from footshocks, such as an aversive noise or one with social behaviors. This is important when considering the goals of intervention when translating from preclinical to clinical populations. Prior work has viewed a decrease in startle responses as an indicator of learning and clinical work has relied on improvements seen in self-reports of anxiety symptomatology. If the concept of “new learning” is considered to be crucial, one would expect this learning to be evident in other behaviors as well, particularly in approach behaviors. From a preclinical perspective, this may include exploring or sniffing the chamber, eating food made available, or lever pressing for rewards (such as saccharin water). In clinical populations, this would include decreased avoidance behavior and increased levels of engagement in meaningful activities. Determining target behaviors to measure and ways to do so procedurally (in both preclinical and clinical investigations) would be a useful area of future attention. This would also support our theoretical understanding of extinction learning and DCSs effects as well as provide further evidence for clinical utility of this treatment adjunct.

While continued research has not garnered as much robust evidence as initially anticipated, it has continued to add to our understanding of the mechanisms and utility of DCS effects by indicating boundary conditions, sub-populations who would most benefit from its use, and supporting the use of post-session administration, and will continue to
be useful. At present, the potential use of DCS as a treatment facilitator is in need of, and continues to be worth, further investigation. In the context of continued interest and further investigation, caution should be kept. As cautioned by Antony (2011), initial enthusiasm for innovation is often greater than warranted by the available data. In the DCS literature, recent research has been met with equivocal results. Regardless of clinical utility, which will continue to be better understood over time, the benefits of this line of research on our understanding of the neurobiological mechanisms of fear learning, extinction, and potential adjuncts to this process are undeniable.
REFERENCES


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Appendix A

Recruitment Flyer
RESEARCH PARTICIPANTS WANTED

You may be eligible to participate in a psychological experiment that includes therapy to address anxiety in social situations and involves giving short, impromptu speeches and studies a newer medication for use with therapy

If you are:

- Anxious in social situations
- Afraid to speak in public
- 18 and older
- Healthy with no current psychological disorders
- Free of any heart problems

Duration: about 13 sessions totaling 12-15 hours of time

Extra credit for participation: If your course instructor permits, you may receive extra credit; there will also be monetary compensation for attendance at follow-up sessions

If interested: Please contact Christina at 387-4332 mailbox 2 or email researchdcs@gmail.com for more information
Appendix B

Classroom Recruitment Script
Classroom Recruitment Script

Hello. My name is (your name), and I am a research assistant in the Anxiety Disorders Lab at Western Michigan University. I’d like to tell you about a project for which we are currently seeking healthy volunteers of age 18 and older that are anxious in social situations and are afraid of public speaking.

The project is intended to study a new medication to be given along with typical therapy for social anxiety. If you are interested and eligible to participate in this project, you will attend individual sessions with a therapist where you will be asked to practice and give impromptu speeches, where you will receive feedback and discuss with the therapist, and will be given either the medication or a placebo pill after each session. You will also be asked to fill out questionnaires about anxiety and participate in a measurement of physiological movements. Your participation will consist of one screening session and 10 treatment sessions, which will take approximately 1 hour each. You will also be asked to attend a follow-up session one month after regular sessions end, and another follow-up session 5 months after that. If your course instructor permits, you may receive extra credit for participation. Participants will also receive monetary compensation for attending the follow-up assessments.

If you are interested in knowing more details, please call the Anxiety Disorders Lab at 387-4332, voicemail box 2 and leave a message for Christina. You can also email the research team at researchdcs@gmail.com. There are also flyers posted on various notice boards, and here is a memo with some contact details if you are interested in participating.

The following will be printed on a 3x3 inch paper and left in the classroom for interested individuals to take:

Investigator: Christina

Anxiety Disorders Lab

Tel: 387-4332 mailbox 2

Email: researchdcs@gmail.com

Project: Slope of Change through DCS Facilitation of Exposure Therapy in a social Anxiety Population
Appendix C

Phone Scheduling Script
Phone Scheduling Script

Hello, is _________ available? When the potential participant comes to the phone, say: Hi, is this _________? If the answer is yes, continue below. If the potential participant is not available, do not leave a message.

Hello my name is (your name) and I’m calling regarding the research study in the anxiety disorders lab about which you had called and left a message. I am calling to give you a little information about the study, to ask you a couple of preliminary questions, and to schedule a meeting to review the consent document. If you would like to learn more about the study, we can schedule a 10-minute meeting so I can give you more details about the study and you can decide whether or not you want to participate.

First, to be eligible to participate in this study, you have to be at least 18 and healthy (free of diagnosed heart problems or psychological conditions), able to swallow pills, experience some form of anxiety in social situations, and not like to speak in public. Do you fit all of those requirements?

If yes, continue below.

If no, say:

Thank you for your interest in this study. But since you are not 18 or older/ have a current psychological/ psychiatric/ medical diagnosis for which you are currently receiving treatment/cannot swallow pills/or don’t mind speaking in public you are not eligible to participate in this study.

This study is designed to look at the differences in improvements in anxiety, apprehension, and fear while going through a therapy protocol with a therapist to target anxiety in social situation, specifically in giving speeches. The purpose of the study is to measure the differences in these responses between participants who take a medication and those who take the placebo. Therefore, if you choose to participate, you will be required to take either the medication or a placebo pill (although neither you nor the experimenter or therapist will be aware of which kind it is) and participate in therapy sessions where you will be asked to practice giving speeches in front of the therapist and research assistants. You will also be asked to answer some questions about your age, health, and any substances you currently use. One thing to keep in mind is that following the screening, you may be told that you are not eligible to participate. The entire screening session will take approximately one hour. Are you still interested in learning more about participating?
If yes, say:
I would like you to come to the Anxiety Disorders Lab for a meeting to give you more details about the study, so that you can decide whether or not you want to participate. And if you decide to participate, will you be available for the assessments to be administered as well?

Which of these dates and times would be convenient for you to come in?

Give prospective subject a list of available times and schedule appointment.

Thank you for your interest in the study. I will see you on (date) at (time) at the Anxiety Disorder Lab. That is, room 2502 on the second floor of Wood Hall. Make sure that prospective participant knows where this is.
Appendix D

Informed Consent for Research Study
Informed Consent for Research Study

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study Title:
Slope of Change through DCS facilitation of Exposure Therapy in a Social Anxiety Population

1.2 Company or agency sponsoring the study:
Western Michigan University, Department of Psychology

1.3 Names, degrees, and affiliations of the researchers conducting the study:
C. Richard Spates, Ph. D.; Professor, Western Michigan University
Christina Sheerin, M.A.; Clinical Psych Graduate Student, Western Michigan University
BK. Ramesh, M.D.; Michigan State University/Kalamazoo Center for Medical Studies

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the research study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.
2. NATURE AND PURPOSE OF THIS RESEARCH STUDY

2.1 Study Purpose:

This research study is intended to compare the effectiveness of a common therapy for social anxiety disorder with the addition of a medication, D-cycloserine (DCS). This study is Christina Sheerin’s dissertation project.

3. RESEARCH STUDY PROCEDURES

3.1 What exactly will be done to me in this study? What kinds of research procedures will I receive if I agree to take part in this study?

The principal investigator of this research study is C. Richard Spates, Ph. D. of Western Michigan University. You will come to weekly therapy sessions at Wood Hall. During these sessions you will fill out assessment questionnaires and will then proceed with therapy. Immediately after the therapy session, you will receive either the DCS or the placebo pill, but you may or may not take the pill after each session.

The therapy will consist of a maximum of 10 individual sessions based on a protocol to address thoughts and behaviors relating to anxiety experienced in social situations. Before every session, you will fill out several self-report questionnaires that will ask you to rate your experiences and emotions. The sessions will consist of discussion of self-monitoring results of practice behaviors engaged in the previous week, problem solving, designing practice exercises and behaviors to work on related to social tasks, and giving speeches in front of an audience of research assistants. At the end of each session, you will give a brief, impromptu speech, during which time other research assistants will also be in the room as an audience and to collect data. These speeches will be videotaped for data collection purposes. Right before giving the impromptu speech, you will be given one final assessment, to measure physiological responses. Three electrodes will be attached with tape to your face and then you will be asked to visualize giving your impromptu speech for 2 minutes. After this assessment, you will give the impromptu speech, and after this speech, the session is finished. One month following therapy sessions, which will consist of a maximum of 10 sessions, a follow up session will take place, where you will fill out assessment measures and engage in an impromptu speech. Another follow-up session will occur 6 months after the final therapy session, and will follow the same format.

3.2 How much of my time will be needed to take part in this study? When will my participation in the study be over?

In addition to the screening assessment, if you choose to participate, the therapy will take place in a maximum of 10 weekly 60 minute sessions. Following the completion of therapy sessions, a one-month and a 6 month follow up session will occur. In total, participation in therapy will take place over about 2-3 months, while the entire participation in the study, if participants go through all assessment sessions, will last about 9 months.
Participation in the research study will be over after the 6 month follow-up session or at any time if you decide that you do not wish to continue with treatment.

In addition to the weekly time devoted to the sessions, participants will be asked to complete some self-monitoring and engage in some practice exposures; this will require an additional hour or so of time during each week.

4. EXPLANATION OF PROCEDURE TO BE FOLLOWED

As mentioned above, therapy sessions will take place as weekly, 60 minute individual sessions. There will be 13 meetings total: 1 assessment/screening session, followed by 10 therapy sessions, followed by a follow-up session 1 month after the last treatment session, and another follow-up session that will take place 6 months after the final treatment session.

Regardless of whether you receive the drug or a placebo you will go through the same therapy. Whether you get the research study drug or placebo will be randomly assigned, a process like flipping a coin. The drug is randomly assigned, meaning that you have a 50% chance of being in the placebo group or the drug group. The research study is a double-blind study, meaning that neither you nor the researcher will know if you have received the study drug, DCS.

Taking part in this research study is completely voluntary. You do not have to participate if you do not want to. You may also leave the study at any time. Refusal to participate in this study will in no way jeopardize your academic standing. If you leave the study before it is finished, there will be no penalty to you and you will not lose any benefits to which you are otherwise entitled.

Your participation in this research study may also be discontinued, without your consent, by the principal or student investigator if, in their opinion, your safety or well-being is in question.

4.2 Who can take part in this study?

Any Western Michigan University student or faculty member, and any community member over the age of 18 who qualifies based on initial screening and assessment.

4.3 How many people (subjects) are expected to take part in this study?

Twenty participants are expected to complete the research study, with about twenty four to twenty six taking part.
5. POTENTIAL BENEFITS

The research study drug being used, DCS, or DCS, is typically prescribed to treat tuberculosis. Recently, it has been used with therapy for anxiety disorders. With this use, it may improve therapy leading to more improvements at a faster rate than exposure therapy alone.

5.1 How could I benefit if I take part in this study? How could others benefit?

One way in which you may benefit from this study is in a reduction in social anxiety symptoms. Regardless of whether you receive DCS or placebo you will be receiving the same psychotherapy treatment. Research has indicated that this psychotherapy protocol for social anxiety disorder, based on speech phobia, is beneficial for individuals who actively participate in therapy.

However, you may not receive any personal benefits from being in this research study.

Participating in research may provide information that may benefit other patients with social anxiety in the future.

5.2 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes. The researchers will tell you if they learn of important new information that may change your willingness to stay in this research study. If new information is provided to you after you have joined the study it is possible that you may be asked to sign a new consent form that includes the new information.

6. POTENTIAL RISKS

6.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

Alcohol will increase your risk of having a seizure during DCS treatment. Alcohol will also increase dizziness and drowsiness. It is important for all participants to avoid alcohol consumption while participating in this study. Do not use alcohol for 2 days before and 3 days after taking a dose of the pill.

Prescription and non-prescription drugs can have serious interactions with DCS; non-prescription drugs should not be taken and prescription drugs should be reported to the study psychiatrist to check for potential interactions.

The medication DCS carries some side effects. Mild side effects may include: headaches, drowsiness, or dizziness. Rare, but more serious side effects that can occur (and will result in discontinuation of medication and leaving the study) include: seizures,
numbness or tingling in your hands or feet, confusion or abnormal behavior, irritability, depression, muscle twitches or tremors (shaking), difficulty speaking, and loss of balance. These effects are indicated for doses of 500 mg per day, a dose higher than what is given in this study. An allergic reaction is possible at any dose of medication. Possible allergies will be screened before medication is given, but seek emergency medical attention or contact Dr. Ramesh immediately if you experience any of the following side effects: difficulty breathing; closing of your throat; swelling of your lips, tongue, or face; hives; or skin rash.

*For more information about the potential side effects and other important information about DCS, please see the Drug Information Handout, attached to this document.

Because of the nature of exposure therapy it is possible that you will experience some discomfort and anxiety during sessions. However, this is normal and should be expected, and is expected to decrease as therapy progresses.

As with any research study, there may be additional risks that are unknown or unexpected.

6.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

In the event that you may be upset by the content of the interview or the therapy protocol, you will be provided with a list of multiple referral sources for therapy, which you may use if you feel that you require assistance. You will be responsible for the cost of therapy if you choose to pursue it.

If an accidental injury occurs or if any side effects of the medication are experienced, appropriate emergency measures will be taken. However, no compensation will be made available except as otherwise specified in this consent form. In the event of an accidental injury, that which occurs while participating in the study in the Anxiety Disorders Lab, the researchers will assist in procuring the necessary aid, but you will not be compensated for emergency costs.

The researchers have taken steps to minimize the known or expected risks by initial screening and weekly check-ins. However, you may still experience problems or side effects, even when the researchers are careful to monitor for side effects. If you believe that you have been harmed, notify the researchers listed in Section 10 of this form. By signing this form you do not give up any of your legal rights as a patient or research subject.

Please note: It is important that you tell the researchers about any injuries, side effects, or other problems that you experience during this study.
7. WOMEN OF CHILDBEARING POTENTIAL

If you are pregnant or breast feeding, you may not participate in this research study. You will take a urine test to see if you are pregnant before you start treatment. If you become pregnant while taking part in this study you agree to inform the study doctor immediately. If you are sexually active, it is strongly recommended that you take precautions to avoid becoming pregnant or fathering a child for the duration of the study because it is not known how this drug could affect an unborn child or infant.

In men, the existence of a potential risk to sperm from use of DCS is unknown.

8. ALTERNATIVE TREATMENTS

8.1 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

8.2 If I decide not to take part in this study, what other options do I have?

Your alternatives would be the University Counseling Center of the WMU Psychology Clinic. The following therapies, which are commonly used, are available as alternatives for the treatment of social anxiety disorder: anti-anxiety medication and other forms of therapy. If after going through therapy, you still feel that you require additional services, the numbers of the above sites will be given to you.

9. PARTICIPANT COMPENSATION

9.1 Will taking part in this study cost me anything? Will I be billed for any costs of the study?

All assessments, therapy sessions, and research study medications for this study are provided to you without charge.

Also see Section 6.2 for reimbursement information for any research related injury.

9.2 Will I be paid or given anything for taking part in this study?

You are not directly paid for participation in the study, but student may receive extra credit points for participating, and all participants are given compensation for attending follow-up sessions. For bonus point opportunities, students will receive a piece of paper signed by one of the researchers verifying your participation that you may give to your instructor.
All participants will also have the opportunity to put their name in a drawing to win a $25 gift card to Target. You will have the opportunity to put your name in the drawing each time you finish a session. You will also be compensated for attending follow-up sessions after the completion of treatment; participants who attend follow-up sessions will each receive $10 per session, in cash. So participants may receive $20 total for attending follow-up sessions; $10 at the 1 month follow-up plus $10 at the 6 month follow up.

10. PHYSICIAN COMPENSATION

10.1 Who could profit or financially benefit from the study results?

There is no financial benefit for the researcher or anyone affiliated with the project; the research study is a dissertation project. Dr. Ramesh, a physician at Michigan State University/Kalamazoo Center for Medical Studies, is participating on a voluntary basis.

11. VOLUNTARY PARTICIPATION/RIGHT TO WITHDRAW FROM THIS RESEARCH STUDY

11.1 If I want to stop participating in the study, what should I do?

You are free to leave the research study at any time. If you leave the study before it is finished there will be no penalty to you and you will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please notify one of the persons listed in Section 12 “Contact Information” (below).

11.2 Could there be any harm to me if I decide to leave the study before it is finished?

There is no harm to leaving the research study at any time, although be aware that without going through the whole protocol, benefits or improvements in social anxiety are not to be expected. In regards to discontinuing the medication, given the low dose and that they are spread out over time, discontinuing the DCS should not lead to problems.

11.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the research study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.
- You experience negative side effects from the DCS medication.
12. CONTACT INFORMATION

12.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the research study
- Ask a question about the study procedures
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: C. Richard Spates, Ph. D.

Mailing Address: Department of Psychology, Room 3700 Wood Hall; Western Michigan University; Kalamazoo, MI 49008-5439

Telephone: (269) 387-4329

Student Investigator: Christina Sheerin, M.A.

Mailing Address: Clinical Psychology, Room 3500 Wood Hall; Western Michigan University; Kalamazoo MI 49008-5439

Telephone: (412) 953-8478

Collaborating Investigator: B.K. Ramesh, M.D.

Michigan State University, Kalamazoo Center for Medical Studies

Telephone: (269) 532-3650

You may also express a concern about a research study by contacting the Institutional Review Board (IRB) listed below. The IRB is a committee that has reviewed this study to help ensure that your rights and welfare as a research subject are protected and that the study is carried out in an ethical manner.

Borgess Medical Center Institutional Review Board
1521 Gull Road
Kalamazoo MI 49048
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the study title (page 1 of this form), and details about the problem. This will help Borgess officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

13. PROTECTED HEALTH INFORMATION (HIPAA)

Borgess Medical Center policies require that private information about you be protected. This is especially true for your personal health information.

On the other hand, sometimes the law allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study.

13.1 How will the researchers protect my privacy?

This authorization is voluntary and any healthcare treatment you may seek will not be conditioned upon your signing this authorization. Signing this form gives the researchers, identified in Section 1.3, your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, as identified in section 6.

Information about you may include information about your health and your medical care before, during, and after the study, even if that information wasn't collected as part of this research study. For example:

- Hospital/doctor's office records, including but not limited to test results (such as, X-rays, lab tests, etc.
- All records relating to your condition, the treatment you have received, and your response to the treatment
There are many reasons why information about you may be used or seen by the researchers or others during this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- Borgess and government officials may need the information to make sure that the study is done properly.
- Safety monitors or committees may need the information to make sure that the study is safe.
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

Applicable federal and state laws protect information used or disclosed pursuant to this consent. However, information that is released may be subject to re-disclosure by the recipient and will no longer be protected by these laws.

13.2 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help Borgess and government officials make sure that the study was conducted properly

If you decide not to give permission to release your personal health information during this informed consent process or before you are enrolled into the research study, you may not be able to participate in the study. This is because the study researcher and/or
his/her/staff would not be able to collect the information needed to fully evaluate the study. If you do not authorize the use and disclosure of your protected health information or cancel it in the future, your current or future medical care will not be affected.

13.3 When does my permission expire?

Your permission expires at the end of the study, unless you revoke it sooner. You may revoke your permission at any time by writing to the researchers listed in Section 12 "Contact Information," but this will not affect uses of disclosures made prior to receipt of the revocation. This means that the data collected up to that point will continue to be used for analysis, and all information remains confidential.

14. RECORD OF INFORMATION PROVIDED

14.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

[ ] This "Informed Consent for Research Study" document. (Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file in the Anxiety Disorders Research Lab.)

[ ] A handout of information DCS and the possible side effects of DCS

15. SIGNATURES (CONSENT)

Research Subject:

I have read this form, discussing the information of the research study investigating the use of DCS for therapy with anxiety disorders. I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with ___________________. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 12 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, I may be asked to re-consent prior to my continued participation in this study.

Signature of Subject: __________________________ Date: ________ Time: ______

Name (Print legal name): __________________________

Participant ID: __________________________ Date of Birth: ________________
Drug Information for DCS (Seromycin)

What is the most important information I should know about DCS?

1. Due to potential side effects that may occur:
   a. Avoid alcohol while taking DCS. Alcohol will increase your risk of having a seizure during DCS treatment. Alcohol will also increase dizziness and drowsiness.
   b. Call Dr. Ramesh immediately (269-532-3650) if you experience a skin rash, mental confusion, dizziness, headache, or tremors (shaking).

What are the possible drug side effects of DCS?

1. If you experience any of the following serious side effects, seek emergency medical attention or contact your doctor immediately:
   a. An allergic reaction (difficulty breathing; closing of your throat; swelling of your lips, tongue, or face; or hives)
   b. Skin rash

2. These symptoms seem to be related to doses of over 500 mg per day, which will not be given during the research study.
   a. Numbness or tingling in your hands or feet
   b. Confusion or abnormal behavior
   c. Tremors (shaking)
   d. Headache
   e. Drowsiness
   f. Dizziness
   g. Difficulty speaking
   h. Irritability

3. Side effects other than those listed here may also occur. Talk to your Dr. Ramesh about any side effect that seems unusual or that is especially bothersome.

What is DCS?

1. DCS is an antibiotic. It prevents tuberculosis bacteria from growing in your body.
2. DCS is used to treat tuberculosis (TB)
3. DCS may also be used for purposes other than those listed in this medication guide, as in the study you may participate in.

Who should not take DCS?

1. You cannot take DCS if you:
   a. Have epilepsy
   b. Suffer from depression
   c. Have a psychotic or psychiatric disorder
   d. Have kidney disease, or
   e. Drink alcohol on a daily basis
   f. Are pregnant or are currently breast feeding
How should I take DCS?

1. A 250 mg pill will be administered one hour before each exposure session.
2. Take each dose with a full glass (8 ounces) of water.

What should I avoid while taking DCS?

1. Avoid alcohol while taking DCS. Do not use alcohol for 2 days before and 3 days after a dose of DCS. Alcohol will increase your risk of having a seizure during DCS treatment. Alcohol will also increase dizziness and drowsiness.
2. Use caution when driving, operating machinery, or performing other hazardous activities. DCS may cause dizziness or drowsiness. If you experience dizziness or drowsiness, avoid these activities.

What other drugs will affect DCS?

1. Before taking DCS, tell your doctor if you are taking
   a. Ethionamide (Trecator-SC) or
   b. Isoniazid (Nydrazid)
2. Drugs other than those listed here may also interact with DCS. Talk to the study doctor and pharmacist before taking any prescription or over-the-counter medicines.

Where can I get more information?

1. Your pharmacist has additional information about DCS written for health professionals that you may read.
2. Also, refer to the phone numbers listed in the informed consent document and contact Dr. Ramesh (269-532-3650) with any questions you may have regarding the drug.

Information obtained from:

Cerner Multum, Inc. 1996-2004; copyright Microsoft, 2008

Physicians Desk Reference, 2008

Your signature below indicates that you have read and/or had explained to you the information on the drug DCS, which you have a 50/50 chance of being given during the research study, and that you agree to participate.

____________________________________  ________________
Signature                                      Date

Consent obtained by: ______________________  ________________
(Initials of researcher)          Date
Appendix E

Screening Questionnaire
Screening Questionnaire

Instructions:
Please read the following statements carefully. If you answer “Yes” to any of the statements, please inform the researcher that you may need to exclude yourself from participation in this study. Please remember that you do not need to inform the researcher as to the specific reason/statement upon which you are excluding yourself.

1. Age: I am younger than 18.
2. There has been a period of time in my life when I had strange/unusual experiences such as:
   a. Seeing or hearing things that other people didn’t notice.
   b. Hearing voices or conversations when no one was around.
   c. Seeing visions that no one else saw.
   d. Had the feeling that something odd was going on around me, or that people were trying to test me, or antagonize or hurt me, so that I felt I had to be on guard constantly.
3. I have a current diagnosis of a medical or psychological disorder and am seeking treatment for it.
4. I am currently receiving treatment specifically to help with public speaking anxiety.
5. I am currently taking medications (excluding birth control and acne medications).
   a. Please list medication and length of time taking each
   b. Are any of the above medications taken for anxiety, stress, or to help you cope with public speaking?
6. I have had a cardiac event, heart problems, irregular heartbeat and/or wear a pacemaker, a stroke, or severe asthma.
7. I have used at least one of the following substances in the past 72 hours:

<table>
<thead>
<tr>
<th>Brand/Generic Names</th>
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<tbody>
<tr>
<td>Bufotenine</td>
<td>Marijuana</td>
<td>Percodan</td>
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<tr>
<td>Cannabis</td>
<td>Marinol</td>
<td>Peyote</td>
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<td>Codeine</td>
<td>MDMA</td>
<td>Phencyclidine: PCP</td>
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<td>Darvon</td>
<td>Methadone</td>
<td>Phencyclidine Hydrochloride,</td>
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<td>Demerol</td>
<td>Meperidine</td>
<td>Phenyl Cyclohexyl Piperidine</td>
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<tr>
<td>Dilaudid</td>
<td>Morphine</td>
<td>Psilocybin: Magic Mushrooms</td>
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<tr>
<td>Dolophine</td>
<td>Numorphan</td>
<td>Talwin</td>
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<td>Dranabinol</td>
<td>Heroin</td>
<td>Thai Stick</td>
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<tr>
<td>Fentanyl</td>
<td>Lysergic acid diethylamide: LSD</td>
<td>Opium</td>
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<tr>
<td>Hash Oil, Hashish,</td>
<td>Oxycodone</td>
<td>Raw Opium</td>
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<tr>
<td>Hydromorphone</td>
<td>Oxymorphone</td>
<td>Sernylan</td>
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<tr>
<td>Hydrocodone</td>
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<td>Vicodin</td>
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**Street Names**

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<tr>
<td>“A”</td>
<td>LSD</td>
<td>Shrooms</td>
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<td>Acid</td>
<td>M and M’s</td>
<td>Smack</td>
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<td>Angel Dust</td>
<td>Magic Mushrooms</td>
<td>Trips</td>
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<td>Cannabis</td>
<td>Marijuana</td>
<td>Weed</td>
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<td>Dope</td>
<td>Mescaline</td>
<td>X</td>
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<td>E</td>
<td>PCP</td>
<td>XTC</td>
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8. I am currently pregnant or breast-feeding.
9. I am unable or find it difficult to swallow pills.
10. I have: kidney disease, epilepsy, severe allergies to prescription medications
11. I am not willing or prepared at this time to tolerate some anxiety during treatment.
Appendix F

Subjective Units of Distress (SUDS) Scale
SUDS Chart

SUDS ratings

Participant # ______ Recorded by __________

SCRIPT: I’d like you to rate your amount of fear and anxiety on a scale from 0 to 100, where 0 is you feel completely calm and relaxed and not anxious at all, 50 is you feel quite anxious and fearful, but you are able to continue fairly easily, and 100 is you are the most anxious and scared you have every been and cannot continue. I am going to have you report on this quite often, before each session, after each session, and every few minutes during your speeches. Do you have any questions at all?

0 -------10-------20-------30-------40-------50-------60-------70-------80-------90-------100
Not anxious Extremely anxious

<table>
<thead>
<tr>
<th>Session #</th>
<th>Time/point in speech (during, after)</th>
<th>SUDS rating</th>
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Appendix G

List of Agencies
List of Agencies

If you would like to explore treatment or intervention services, below is a list of agencies you can contact.

Family & Children Services  269-344-0202

Psychology Clinic at Western Michigan University  269 387-8302

The Center For Counseling and Psychological Services at Western Michigan University  269-387-5105

The WMU Counseling Center:  269-387-1850

Mid-America Psychological Services PC  269-327-1438

Cognitive Behavior Solutions PLC  269-779-6001

Kalamazoo Community Mental Health  269-373-4951; Crisis Hotline: 888-373-6200
Appendix H

Verification of Participation in Research
Verification of Participation in Research

This is to certify that (name) ______________________participated as a research subject in the study within the Anxiety Disorders Laboratory” on _____________ for ________ hours.

Signature of researcher/research assistant: ______________________
Appendix I

Patient Screening Document
Patient Screening Document

Patient Screening Document; to be administered by the physician

**Hypersensitivity:**
Have you ever had a reaction to any medications?
Have you ever had a rash from any medications?
Have you ever had to stop any medications?
Has anyone in your family told you about a medication reaction?
Have you ever had an allergic reaction to foods? Like sea foods?
Have you ever had a reaction to OTC medications?

**Epilepsy:**
Have you ever had a seizure?
Have you ever taken any medications for seizure?
Have you ever had periods of time that you cannot account for?
Has anyone ever told you that you acted strange and you could not remember doing so?
Have you ever had unexplained bruises or bit your tongue without knowing the reason?
Have you ever had an EEG (Brain Wave) done?
Have you ever had a brain scan?
Has anyone in your family had epilepsy or seizures?

**Psychiatric:**
Have you ever been in mental health treatment?
Have you ever seen a psychiatrist?
Have you ever seen a counselor, therapist, or psychologist?
Has your family physician prescribed medication to help with depression?
Have you been on any medications for your “nerves”?
Have you ever lost touch with reality?
Have you ever heard or seen things that others did not?
Have you ever gotten special personal messages from the TV or radio?

Have you ever been on:

Prozac
Zoloft
Paxil
Effexor
Xanax
Ativan
Klonopin
Zyprexa
Seroquel
Risperidal
Depakote
Neurontin
Other drug for mental symptoms

Have you ever been hospitalized on a psychiatric unit?

Renal:

Do you have a history of kidney disease?

Have you ever seen a kidney specialist?

Have you ever had blood in your urine?

Have you ever been told you had abnormal kidney function or blood work?

Have you ever had pain or discomfort on urination?

Have you ever been told you have sugar or protein in your urine?

Have you ever had dialysis?

Alcohol:

When did you last drink alcohol?

How often do you typically drink alcohol?

7 times a week
6 times a week
5 times a week
4 times a week
3 times a week
2 times a week
1 time a week
Less frequently
How much do you drink at a time?
1 to 2
2 to 3
More than 3

Has alcohol ever been a problem for you?

Have you ever been treated for alcoholism?

Has anyone ever told you that you drink too much?

Have you ever had liver problems?

Have you had abnormal blood work results after drinking alcohol?

Have you ever lost a job because of alcohol use?

**Cardiovascular:**

Do you have any heart disease?

Have you ever been told you had heart failure?

Have you ever had swelling of both ankles?

Are you short of breath other than briefly after extreme exertion?

Do you take any medications for your heart?

Have you ever been on a water pill?

Have you ever seen a heart specialist?

**Pregnancy:**

Is it possible that you could be pregnant?

Results of pregnancy test:
Appendix J

Script for Facial EMG Recording
Script for Facial EMG Recording

Now I would like you to close your eyes and imagine yourself giving the speech that you have just prepared. I would like you to picture in detail the room, the faces of the audience, and how you are feeling as you stand in front of the audience. I would like you to keep your eyes closed and keep that image in mind until I ask you to stop.

Now please keep your eyes closed but you may stop imagining this scene. Please sit for another minute until I tell you that you may open your eyes.
Appendix K

Human Subjects Institutional Review Board
Letter of Approval
Date: January 19, 2012

To: C. Richard Spates, Principal Investigator
    Christina Sheerin, Student Investigator for dissertation

From: Amy Naugle, Ph.D., Chair

Re: HSIRB Project Number 11-09-04

This letter will serve as confirmation that your research project titled “Slope of Change through DCS Facilitation of Exposure Therapy in a Social Anxiety Population Slope of Change through DCS Facilitation of Exposure Therapy in a Social Anxiety Population” has been approved under the full category of review by the Human Subjects Institutional Review Board. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note that you may only conduct this research exactly in the form it was approved. You must seek specific board approval for any changes in this project. You must also seek reapproval if the project extends beyond the termination date noted below. In addition if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the HSIRB for consultation.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: September 21, 2012
December 21, 2011

C. Richard Spates, PhD
Christina Sheerin
3500 Wood Hall, Psychology Department
Western Michigan University
Kalamazoo MI 49008

Protocol – Slope of Change through DCS Facilitation of Exposure Therapy in a Social Anxiety Population
BMC IRB Reference No. 2011-27:73
Informed Consent: 11/8/11

Dear Dr. Spates and Ms. Sheerin,

The Institutional Review Board of Borgess Medical Center reviewed the above-named protocol at their meeting on September 20, 2012. Based upon that review and your personal presentation, the Committee agreed that the protocol met our standards of research and approved the study and consent form for use in this institution.

As you conduct your research, you are responsible for complying with all policies and procedures of the FDA, OHRP, HIPAA, Borgess Medial Center, and the Borgess Institutional Review Board. Per the Borgess Health policy “Research Approval Process” (BH.303), protocols must go through all appropriate research oversight committees (Research Financial Conflict of Interest, Research Billing Committee, etc.).

The approval is granted with the understanding that any changes in the protocol are promptly reported to the Committee; that changes in the approved protocol cannot be initiated without Committee review and approval unless there are immediate hazards to human subjects; and that all unanticipated or serious problems involving risks to human subjects are also promptly reported to the Committee.

Approval for this protocol is granted for a period of one year and will expire on September 18, 2012. The FDA and this Committee, require you submit in writing a Continuation Review Application by September 4, 2012. The protocol cannot continue after September 18, 2012 until re-approved by the Borgess IRB even if closed to patient enrollment. You must complete a Close Out Report if your protocol has been completed, terminated or if you are not renewing the protocol. We will determine if the research was carried out as planned, and that patient benefit outweighed the risk. A copy of each signed IRB approved consent form is required.

If you have any questions in this regard, please feel free to contact me.

Sincerely,

Elaine Van Doren, PhD, RN
Chair Pro Tem
Institutional Review Board