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D-cycloserine enhancement of exposure therapy for social anxiety disorder depends on the success of exposure sessions

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ABSTRACT

Objective: The evidence for the efficacy of D-cycloserine (DCS) for augmenting cognitive behavioral therapy (CBT) for anxiety disorders has been mixed. Guided by preclinical research and initial findings from a small-scale study involving humans, we tested the hypothesis that DCS enhancement of exposure therapy would be specific to successful exposure sessions.
Method: Medication-free adults with generalized social anxiety disorder ($N = 145$) received 50 mg of DCS or placebo 1 h before each of 5 exposure sessions that were part of a standardized 12-session group CBT protocol. Participants provided fear ratings at the beginning and just before the end of exposure exercises. Independent raters, blind to group assignment, administered the clinical global impression improvement and severity scales at each session and at posttreatment.
Results: Mixed-effects analyses revealed that, among patients who reported low fear at the end of an exposure session, those who had received DCS evidenced significantly greater clinical improvement at the next session, relative to those who had received placebo. In contrast, when exposure end fear was high, patients receiving DCS exhibited less clinical improvement at the following session than patients receiving placebo. Similarly, patients who had received DCS evidenced lower clinical severity at posttreatment, relative to patients who had received placebo, only when their average end fear for medication-augmented sessions had been in the low to moderate range. Finally, these moderating effects of exposure success as indexed by end fear were not better accounted for by within-session extinction.
Conclusions: The efficacy of DCS for augmenting exposure-based CBT depends on the success of exposure sessions. These findings may help guide the development of an algorithm for the effective use of DCS for augmenting exposure-based CBT.
Trial registry: http://www.ClinicalTrials.gov, ID# NCT00633984, http://www.clinicaltrials.gov/ct2/show/NCT00633984.

1. Introduction

One particular success of translational research is the investigation of D-cycloserine (DCS), a partial agonist of the glycine recognition site of the N-Methyl-D-Aspartate receptor (NMDAr), as an augmentation strategy for exposure-based cognitive behavioral therapy for the anxiety disorders (Davis et al., 2006; Hofmann et al., 2011). Following a series of studies indicating that extinction learning is NMDAr dependent (see Davis et al., 2006), Davis and colleagues first demonstrated that DCS can enhance retention of fear extinction in rats and subsequently showed that DCS enhances the outcome of extinction-based therapy (i.e., virtual reality exposure therapy) for height phobia (Davis et al., 2006). These initial findings created great excitement among anxiety disorder treatment researchers who have been faced with the challenge to improve the outcomes of exposure-based CBT for anxiety disorders

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such as social anxiety disorder (Hofmann and Smits, 2008), which are prevalent and associated with significant personal and economic costs (Greenberg et al., 1999; Kessler et al., 2005). Not surprisingly, the last several years have seen a number of studies evaluating the efficacy of DCS for enhancing outcomes for exposure-based CBT (Hofmann et al., 2011).

The efficacy of D-cycloserine (DCS) for enhancing exposure therapy has been variable across these studies, with several evidencing strong augmentative effects of DCS (Guastella et al., 2008; Hofmann et al., 2006; Otto et al., 2010; Ressler et al., 2004), and several showing either relatively weak effects (Kushner et al., 2007; Wilhelm et al., 2008), no effects (Guastella et al., 2007; Storch et al., 2007; Tart et al., 2013), or even detrimental effects (Litz et al., 2012). Animal research has pointed to the adequacy of extinction training, as indexed by sufficient decrement in fear responding during the training session, as a potential moderator of the augmentation effects of DCS. Indeed, in re-analyses of null findings, Weber and colleagues (Weber et al., 2007) and Bouton and colleagues (Bouton et al., 2008) demonstrated that the efficacy of DCS for facilitating extinction retention was evident only in animals that had demonstrated a large decrement in fear responding during extinction training.

Analogous to these animal studies, we recently reanalyzed a null finding for DCS augmentation from a small-scale trial involving patients ($N = 29$) undergoing exposure therapy for height phobia. The original analyses revealed that patients receiving 50 mg of DCS administered following each of two sessions of 30 min of hierarchical virtual reality exposure did not evidence better clinical outcomes than patients receiving identical exposure combined with placebo (Tart et al., 2013). In our reanalysis of these findings (Smits et al., 2013b), we tested whether the effects of DCS administration on subsequent clinical improvement would be moderated by the relative success of the exposure session. Because the exposure session was delivered in a hierarchical fashion (i.e., gradually moving up a simulated glass elevator), we indexed exposure success (or decrement in fear responding) using the fear level that patients reported at the end of the session, while controlling for baseline severity, the number of floors completed in the exposure hierarchy, and the level of fear reported at the beginning of the exposure session. Consistent with the findings from animal studies (Bouton et al., 2008; Weber et al., 2007), the result of this reanalysis showed that DCS facilitated clinical improvement when patients ended their previous exposure session with low fear levels, and, conversely, inhibited clinical improvement when patients ended their previous exposure session with elevated fear levels (Smits et al., 2013b). Assuming clinicians accurately targeted patients' fears with challenging exposure assignments, low end fear provides a measure of extinction success, consistent with preclinical studies (Lee et al., 2006). Replication and extension of this potential marker for the successful use of DCS has important implications for the clinical application of DCS augmentation strategies.

The present paper represents the first reanalysis of a large-scale trial of DCS augmentation. Specifically, in the largest clinical trial of DCS augmentation published to date, Hofmann et al. (Hofmann et al., 2013) found that DCS augmentation of exposure-based CBT for social anxiety disorder resulted in faster, but not greater, treatment response than placebo augmentation. Based on the extant research, we hypothesized that the relative advantage conferred by DCS administration on clinical improvement would be moderated by the success of the exposure session, such that advantage of DCS over placebo with respect to clinical improvement would be greater following sessions characterized by low end fear levels than following sessions characterized by elevated end fear levels. Building further upon our previous study (Smits et al., 2013b), we also explored in this paper the possibility that within-session extinction (i.e., peak fear minus end fear), an alternative operationalization of exposure success (Smits et al., 2013b), is a more critical dimension for moderating the efficacy of DCS than end fear.

2. Materials and method

2.1. Participants

Participants in the trial were 169 adults with a diagnosis of generalized SAD utilizing the Structured Clinical Interview for DSM-IV Diagnosis (First et al., 2001) and a score of 60 or higher on the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987). Exclusion criteria included (a) medical disorders of clinical significance; (b) lifetime history of obsessive-compulsive disorder, bipolar disorder, schizophrenia, psychosis, or delusional disorders; (c) diagnosis within the past 6 months of post-traumatic stress disorder, eating disorders, or substance abuse or dependence; (d) organic brain syndrome, mental retardation, or other cognitive dysfunction; (e) current suicidality and/or clinically significant suicidal behavior or ideation within the past 6 months; (f) concurrent psychotropic medication, concurrent psychotherapy, or prior non-response to adequately delivered exposure therapy; and (g) women who were pregnant, breastfeeding, or planning to become pregnant. This study reports on the 145 patients who provided in-session fear ratings (see Fig. 1).

2.2. Study procedures

As reported previously (Hofmann et al., 2013), participants were screened for eligibility and then enrolled in the study at one of three sites: Boston Massachusetts General Hospital (MGH), Boston University (BU), or Southern Methodist University (SMU). The Institutional Review Boards at MGH, BU, and SMU approved the study protocol and all participants provided written informed consent. Participants then began a 12-session CBT protocol, during which they were randomized at session 3 to receive either DCS or pill placebo an hour prior to sessions 3–7. Randomization was performed in a double-blind fashion using a computer-generated allocation schedule which stratified participants by baseline LSAS severity ratings ($\leq$70 or $\geq$70; Liebowitz et al., 1992). Self-reported ratings of beginning fear, end fear, and peak fear were obtained for each exposure session. Clinical status and improvement were assessed by an independent rater, blind to group assignment, prior to treatment sessions and pill administration (at baseline, weeks 2–8, 10, and 12), at posttreatment (week 13), and follow-up (at 1, 3, and 6 months posttreatment). This manuscript reports on data collected at baseline, during the treatment phase and at posttreatment.

2.2.1. Cognitive behavioral therapy

The intervention approach was based on a 12-week CBT treatment protocol involving weekly 2.5-h sessions (Heimberg and Becker, 2002), but drew heavily from the strategies outlined by Hofmann and Otto (Hofmann and Otto, 2008) based on the model described by Hofmann (2007). The first two sessions were psychoeducational, describing the nature of SAD, providing the treatment rationale, and introducing the concept of cognitive restructuring. Participants completed exposure exercises in sessions 3–7, consisting of prolonged public speaking, with the goal of fear extinction. Given that public speaking ranks high in the hierarchy of feared situations in patients with generalized SAD, we opted to focus mostly on public speaking during the exposure sessions 3–7. This is similar to previous studies from our group (e.g., Hofmann, 2004; Hofmann et al.2006), which have shown