BRIEF REPORT

D-Cycloserine Augmented Exposure Therapy for Obsessive-Compulsive Disorder

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Background: D-cycloserine (DCS), a glutamatergic partial N-methyl-D-aspartate (NMDA) agonist, can facilitate extinction learning related to cued fear in animals and humans. We predicted that DCS would accelerate obsession-related distress reduction in patients with obsessive-compulsive disorder (OCD) undergoing extinction-based exposure therapy.

Methods: We administered DCS (125 mg) or placebo in a double-blind fashion to individuals with OCD approximately 2 hours before each exposure session.

Results: D-cycloserine decreased both the number of exposure sessions required to achieve clinical milestones and the rate of therapy dropout. After four exposure sessions, patients in the DCS group reported significantly greater decreases in obsession-related distress compared with the placebo group; however, after additional sessions, the placebo group tended to catch up.

Conclusions: D-cycloserine augmentation has the potential to increase the efficiency, palatability, and overall effectiveness of standard exposure therapy for OCD.

Key Words: Cognitive-behavioral therapy, D-cycloserine, obsessive-compulsive disorder, treatment

Rodents given the *N*-methyl-D-aspartate (NMDA) receptor partial agonist, D-cycloserine (DCS) demonstrate accelerated extinction learning (Richardson *et al.* 2004; Walker *et al.* 2002)

Because nearly complete elimination of conditioned fear responding is possible given a sufficient number of extinction trials ("floor effect"), DCS effects are maximally detectable early in extinction training (Walker *et al.* 2002). D-cycloserine was also found to improve response to two to four sessions of extinction-based ("exposure") therapy in patients with social phobia and acrophobia (Hofmann *et al.* 2006; Ressler *et al.* 2004, respectively). However, Guastella *et al.* (in press) found no such effect in "spider fearful" individuals, perhaps suggesting that the benefits of DCS augmentation in humans may be restricted to phobia-level fears.

Based on the earlier work, we predicted that DCS would also facilitate the capacity of exposure therapy to weaken the link between obsession-related stimuli (e.g., public restrooms) and feared outcomes (e.g., contamination), thereby reducing associated fear responding (e.g., distress) along with the need for rituals (e.g., washing) and avoidance. In keeping with the aforementioned human DCS exposure protocols and the potential for extinction floor effects, we predicted that these DCS effects would be apparent after only four sessions (versus the 10 to 15 sessions typical in obsessive-compulsive disorder [OCD] therapy) (Riggs and Foa 1993). Finally, we predicted that more rapid progress associated with DCS would enhance patient motivation leading to fewer therapy dropouts.

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Methods and Materials

Subjects

One hundred fifty responses to newspaper ads included 63 individuals who failed to meet inclusion/exclusion criteria and 55 who chose not to participate or could not be contacted. Thirty-two individuals enrolled and attended at least one therapy session (DCS group $n = 15$, placebo group $n = 17$), with 25 individuals completing the treatment (DCS group $n = 14$, placebo group $n = 11$). Inclusion criteria were a diagnosis of OCD by the Structured Clinical Interview for DSM-IV (First *et al.* 1989) and a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score ≥18 (Goodman *et al.* 1989). Extra-study psychiatric medications were allowed if dose was stable for at least 2 months prior to the study. We excluded individuals for whom hoarding or ordering rituals were primary (as per the hypothetical role of DCS as a facilitator of fear-based extinction learning) and those who met criteria for current major depression (MD) or substance use disorder (SUD) or were pregnant, lactating, or at risk of becoming pregnant. Written informed consent was obtained from all subjects after the Institutional Review Board (IRB)-approved protocol was explained.

Medication

We dispensed to each subject 10 doses of 125 mg DCS or 10 identical-looking placebo doses in a random double-blind fashion.[1] The research assistant confirmed by phone that all subjects

[1]The fact that the therapy enhancing properties of DCS were similar for 50 mg and 500 mg in the Ressler study suggested to us two possibilities: 1) that any dose within this range is equally effective in enhancing exposure therapy response; or, 2) that there is a curvilinear relationship between dose and degree of exposure therapy enhancement. From the standpoint of the latter possibility, the Ressler *et al.* data would be interpreted to say that 50 and 500 mg represent roughly the same level of impact on exposure therapy, albeit along the ascending vs. descending limb (respectively) of a curvilinear efficacy continuum. This is theoretically consistent with the curvilinear impact of DCS on NMDA neurotransmission; i.e., with lower doses acting as a partial agonist and higher doses acting as an antagonist (e.g., Quartermain *et al.*, 1994). If this were true than a dose somewhere between 50 and

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took one dose of study medication approximately 2 hours prior to each session.

Exposure/Ritual Prevention Therapy

Exposure/ritual prevention (EX/RP) therapy techniques conformed to standard cognitive behavioral therapy (CBT) practice (e.g., Riggs and Foa 1993) and were delivered twice weekly by a trained psychologist. At baseline, we identified and listed a hierarchy of subjects' 10 most disturbing obsession-related stimuli (e.g., touch a toilet seat). At every session, the patient rated each hierarchy item from 1 (none) to 100 (maximum) on the Subjective Unit of Distress Scale (SUDS). Early exposure exercises focused on items with lower initial SUDS ratings. Once a rating was reduced by at least 50%, a more difficult exercise was introduced until all SUDS ratings were reduced by 50% (of baseline) or until the 10th session, whichever came first.[2]

Y-BOCS

The Y-BOCS was given at baseline, after the fourth session, at the last session, and at 3-month follow-up.

Results

Baseline

Severity of illness was highly similar between the groups, as evidenced by baseline Y-BOCS (DCS, M = 27.1, SD = 3.8 vs. placebo, M = 28.2, SD = 5.1) and hierarchy SUDS ratings (DCS, M = 82.6, SD = 12.8 vs. placebo, M = 85.4, SD = 9.4) Both *t* values were not significant (*p*'s =.47 and .49, respectively). Extra-study medication use was also similar (χ^2, p = .76) between the groups (DCS = 64.3% vs. placebo = 58.8%). A board-certified psychiatrist who was blind to group identified four placebo subjects (23.5%) and two DCS subject (13.3%) who had an adequate type and dose of medication for a "typical" OCD treatment at entry to the study (χ^2, p = .28). There was a nonsignificant trend ($p < .07$) for the noncompleters (n = 7) to have higher baseline Y-BOCS scores (M = 30.4, SD = 4.5) than completers (n = 25; M = 26.9, SD = 4.1).

Side Effects

D-cycloserine was well tolerated with reports of mild gastrointestinal (GI) distress (1), dizziness (1), fatigue (1), and anxiety (1). The placebo group also reported "jittery feelings" (1), dissociation (1), and dry lips (1).

EX/RP Completion/Compliance

Seventy-eight percent of the entire sample completed the EX/RP therapy (see Footnote 2). However, this was true for 93.3% of DCS subjects versus 64.7% of placebo subjects [$\chi^2(1)$ = 3.82, $p < .05$; Fisher exact test, p = .09]. Therapy compliance, as rated blindly by the study therapist, was high (above 90%) for both groups.

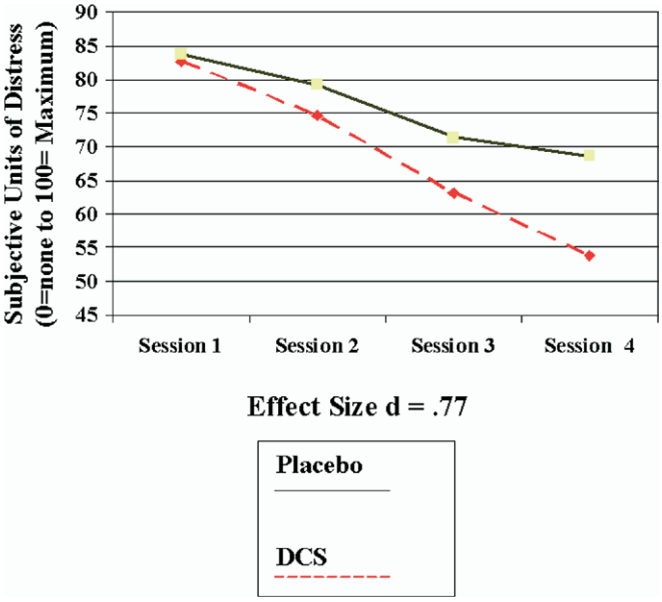

Figure 1. Change in mean obsession-related fear over four sessions.

Outcomes Through Four Exposure Sessions. As predicted, obsession-related fear ratings declined more rapidly in the DCS group compared with the placebo group over four EX/RP sessions [$F(3,21) = 4.11$, $p < .02$; d = .77] (Figure 1). Post hoc group comparisons at each session found significant differences only at session 4 (t = 2.3, $p < .05$). A separate analysis of variance (ANOVA) showed there was a significant EX/RP (time) effect for Y-BOCS after four sessions [$F(1,23) = 101.44$, $p < .0001$]; however, contrary to expectations, there was no group by time (i.e., baseline to postsession 4) interaction on Y-BOCS (DCS session 4, M = 15.1, SD = 4.8 vs. placebo session 4, M = 15.5, SD = 6.2).

Outcomes Through Last Session and Follow-up.[3] On average, those in the DCS Group reached the >50% SUDS reduction criterion (see Methods and Materials) on all hierarchy items in about two fewer sessions than those in the placebo group (Figure 2). Survival analysis (Kaplan-Meier) of completers showed this effect was significant [log rank = 3.71(1), p = .05]. However, by the time subjects reached their last session, SUDS level was no longer significantly different [$t(23) = 1.08$, p = .29; DCS, M = 31.4, SD = 18.0; placebo, M = 39.1, SD = 17.7], indicating that this DCS effect was concentrated in the earlier sessions. The Y-BOCS score was also not significantly different between the groups at the last session (DCS, M = 10.9, SD = 4.7 vs. placebo, M = 11.2, SD = 6.8) or at the 3-month follow-up (n = 18; placebo, M = 11.3, SD = 6.7; DCS, M = 12.3, SD = 7.2).

500 mg would offer more benefit than either 50 or 500 mg. Given these possibilities, we felt that 125 mg offered no risk of being outside the empirically established therapeutic range identified by Ressler and colleagues while also offering the theoretical possibility of being superior to either of the two doses those researchers employed.

[2]Although our hypotheses focused on four sessions of EX/RP therapy (see Introduction for rationale), we provided up to 10 EX/RP sessions (the standard number of sessions delivered in our outpatient OCD clinic) on the ethical grounds that all subjects should have access to treatment as usual (TAU) if needed; especially those in the Placebo Group who were not expected to clinically benefit by fewer than 10 sessions. However, we also established an a priori clinical criterion (i.e., all hierarchy ratings reduced by 50%) to identify a rapid (i.e., < 10 sessions) treatment response; especially among those in the DCS group who we hypothesized would require fewer than 10 sessions to obtain a good clinical outcome.

[3]Because subjects potentially completed the therapy at different rates (see Method section and Footnote 2), comparing the groups at subjects' last session (vs. at session 10) provided a more sensible and inclusive endpoint. An alternative we considered was to carry the last observation forward to the 10th session for those completing the therapy in less than 10 sessions; however, we rejected this approach because it was more speculative than the approach we adopted.

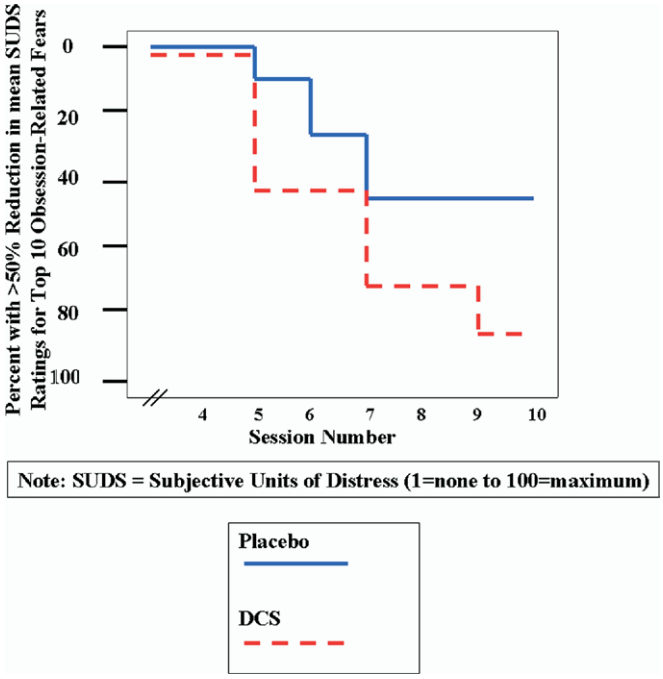

Figure 2. Time to >50% reduction in obsession-related fears.

Discussion

As predicted, DCS promoted extinction of obsession-related distress in response to four sessions of exposure therapy. This replicates findings in the clinically less complex anxiety disorders, social phobia and acrophobia (Hofmann *et al.* 2006; Ressler *et al.* 2004). D-cycloserine may have exerted this effect by enhancing the generalization (Ledgerwood *et al.* 2005) and/or efficiency (e.g., Walker *et al.* 2002) of extinction learning. Although not known with certainty, the prevailing view is that DCS facilitates extinction by enhancing long-term potentiation (LTP) via agonist action at the NMDA glycine-binding site (e.g., Miller 2004; Watanabe *et al.* 1992).

We also found that those given DCS were about one sixth as likely to drop out of the EX/RP therapy as those given placebo (6% vs. 35%). This effect may be secondary to the more favorable effort to benefit ratio for exposure therapy that DCS provided in the early sessions. In any case, this finding suggests that DCS has the potential to increase the actual effectiveness of EX/RP therapy by reducing the approximately 25% of OCD cases that otherwise tend to avoid or quit this therapy (e.g., Riggs and Foa 1993).

Our having allowed up to 10 EX/RP sessions (see Footnote 2) might explain the absence of DCS effects on the Y-BOCS. Had we stopped the EX/RP therapy at session 4 when the DCS effect on obsession-related fear was maximal—as did Ressler *et al.* (2004) and Hofmann *et al.* (2006)—the DCS group might have had the opportunity to ultimately develop superior outcomes on a wider range of OCD symptom dimensions. For example, reduced fear at treatment end should lead to greater self-exposure and reduced negative reinforcement from the practice of rituals. This suggests a treatment protocol in which DCS-augmented exposure therapy is relatively brief (<5 sessions).

Another explanation for decreasing DCS effects after session 4 relates to the potential paradoxical antagonist NMDA effects that have been observed at high and/or chronic DCS doses (e.g., Quartermain *et al.* 1994). Accordingly, twice weekly DCS administration might have altered DCS action at the receptors producing increasingly paradoxical effects in later relative to earlier sessions. This possibility suggests a treatment protocol that uses the lowest effective dose of DCS (perhaps 50mg) (see Footnote 1) and spaces sessions further apart than semiweekly (past studies utilized once weekly sessions).

Our findings suggest that the degree to which DCS promotes extinction in OCD after four exposure sessions (d = .77) is about the same as in social phobia (d's = .73, .72, .98) (Hofmann *et al.* 2006) and acrophobia (d's = 1.06, 1.00) (Ressler *et al.* 2004). This may reflect commonalities in neural underpinnings of anxiety, fear, and distress components between OCD and other anxiety conditions (e.g., Rauch *et al.* 1997). Alternatively, obsession-related distress may be neurologically distinct from phobic fears, while DCS promotes extinction learning across a range of conditioned responses beyond fear per se (e.g., Botreau *et al.* 2006). Also, our data do not allow us to clarify whether DCS effects were specific to OCD symptoms versus a reduction in stress responding more generally; although, past studies (e.g., Walker *et al.* 2002) do rule out direct anxiolytic effects for DCS given in the absence of specific extinction procedures.

A limitation to the study is that comorbidities other than MD and SUD were not assessed and so could not be compared between groups. Future efforts to establish an optimal DCS-exposure treatment protocol will also have to consider how to incorporate selective serotonin reuptake inhibitor (SSRI) medication treatment. In the present study, about 16% of the sample were deemed (by history) to be nonresponders to adequate psychiatric medication treatment, primarily SSRIs. The absence of significant main effects or interactions between medication nonresponder status and study group suggests that a DCS-exposure protocol could be implemented along with conventional medication treatment for OCD and may provide benefit to those who are nonresponsive to standard medication treatments.

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