A Meta-Analysis of D-Cycloserine and the Facilitation of Fear Extinction and Exposure Therapy

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Background: Translational research suggests that D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) receptor agonist, might facilitate fear extinction and exposure therapy by either enhancing NMDA receptor function during extinction or by reducing NMDA receptor function during fear memory consolidation. This article provides a quantitative review of DCS-augmented fear extinction and exposure therapy literature.

Methods: English-language journal articles that examined DCS augmented with fear extinction or exposure therapy were identified through public databases from June 1998 through September 2007, through references of originally identified articles and contact with DCS investigators. Data were extracted for study author, title, and year; trial design; type of subject (animal vs. human; clinical vs. nonclinical); sample size, DCS dose, and timing in relation to extinction/exposure procedures; dependent variable; group means and SDs at post-extinction/exposure; and follow-up outcome.

Results: D-cycloserine enhances fear extinction/exposure therapy in both animals and anxiety-disordered humans. Gains generally were maintained at follow-up, although some lessening of efficacy was noted. D-cycloserine was more effective when administered a limited number of times and when given immediately before or after extinction training/exposure therapy.

Conclusions: This meta-analysis suggests that DCS is a useful target for translational research on augmenting exposure-based treatment via compounds that impact neuroplasticity. D-cycloserine 's major contribution to exposure-based therapy might be to increase its speed or efficiency, because the effects of DCS seem to decrease over repeated sessions. This information might guide translational researchers in discovering more selective and/or effective agents that effectively enhance (or reduce) NMDA receptor function.

Key Words: Anxiety, D-cycloserine, exposure therapy, extinction, glutamate, neuroplasticity, NMDA

A growing body of evidence suggests that the extinction of fear is mediated by N-methyl-D-aspartate (NMDA) receptor activity in basolateral amygdala (1–7). The NMDA glutamate receptor function can be enhanced indirectly and safely by stimulation of the high-affinity glycine binding site, a feature of the NMDA glutamate receptor complex (8). D-cycloserine (DCS) is a partial agonist of the glycine site and indirectly increases glutamatergic activity in previously "silent" synapses (9). Nevertheless, DCS has complex modulatory actions at NMDA glutamate receptors. When surrounding glycine levels are low, it facilitates NMDA receptor function with up to approximately 60% of the efficacy of glycine, but when glycine levels are sufficient to saturate $glycine_B$ sites, DCS might reduce NMDA receptor function by as much as 40%–50% (10–12). Therefore, DCS might improve the efficacy of exposure-based psychotherapies by enhancing NMDA receptor functioning, thereby increasing neuroplasticity or by reducing NMDA receptor function and interfering with the (re)consolidation of fear memories. Both processes are thought to facilitate fear extinction (13).

Studies of fear extinction in animals suggest that DCS might increase or accelerate extinction effects. In one study by Walker *et al.* (14), rats were conditioned to exhibit a startle reflex toward a light after the light was paired repeatedly with a foot shock. Rats were injected with either saline or DCS (15 mg) and tested with or without extinction training (light exposure without shock). Only rats that received DCS in addition to extinction training showed a reduction in fear-potentiated startle; rats that received DCS without extinction training did not benefit. In a follow-up experiment, injection of a glycine site antagonist, HA-966, blocked DCS extinction enhancement. These results suggest that the facilitative effects of DCS are not due to any anxiety-attenuating properties but rather to the mediation of the neural mechanisms of extinction. In another experiment performed by these authors, DCS was associated with a dose-dependent enhancement of extinction effects. Rats that received moderate (15 mg/kg) or high (30 mg/kg) DCS doses showed a greater extinction effect (less startle) than those who received a low-dose DCS (3.25 mg/kg); however, there were no differences between rats that received moderate and high DCS doses, suggesting that a moderate dose is sufficient to facilitate extinction. A subsequent study (15) extended the findings of Walker *et al.* (14) with lower DCS doses. At lower doses (2.5, 5, and 10 mg/kg), a dose-response relationship was found when DCS was administered immediately after extinction training. This finding suggests that DCS facilitates extinction by acting on memory consolidation processes that take place after training.

Given the similarity between fear extinction training in animals and exposure-based psychotherapy in humans, translational research from preclinical to clinical work has begun with DCS. In the first study with humans, Ressler *et al.* (16) reported that DCS administration did not affect baseline subjective fear levels in patients receiving virtual reality exposure therapy for specific phobia of heights, replicating the animal findings that the effects of DCS are not due to anxiolytic properties. Patients receiving either 50 or 500 mg DCS seemed to benefit more from virtual reality exposure therapy than patients receiving placebo (PBO). These results have been replicated and extended with 50 to 125 mg of DCS in combination with exposure therapy for patients with social anxiety, panic, and obsessive-compulsive disorder (OCD) (17–20).

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As the preclinical and clinical studies demonstrating the ability of DCS to augment extinction/exposure therapy accumulate, there is a growing need for a succinct review of this literature. Numerous qualitative reviews of this translational research have identified DCS as a pharmacological agent that facilitates extinction learning in rats and potentially exposure therapy with anxiety-disordered humans (7,21–31). A quantitative description of this literature could allow for stronger inferences to be made regarding the ability of DCS to improve extinction/exposure therapy and provide methodological suggestions for future research.

The present study employed meta-analytic strategies (32) to examine the literature on the ability of DCS to facilitate fear extinction/exposure therapy. Specifically, the effects of fear extinction/exposure therapy combined with DCS were compared with the effects of fear extinction/exposure therapy combined with PBO at post-treatment and follow-up. The effects of DCS also were compared between animals and humans and between nonclinical/subclinical participants and anxiety-disordered humans. Lastly, the moderating effects of dose, dose timing, and number of dose sessions were explored.

Methods and Materials

Data Sources

Journal articles were identified through searches of the Medline and PsychINFO electronic databases from June 1998 through September 2007 with the search terms [(DCS or D-Cycloserine) and (extinction or exposure therapy)] and restricting to the English language. Relevant studies also were identified through references of originally identified articles and contact with DCS investigators. This literature search identified 44 articles, which then were examined for inclusion.

Study Selection

Randomized, PBO-controlled trials were included if: 1) sufficient information was provided to compute effect sizes (or necessary additional information was supplied by the authors) and if they 2) examined DCS augmented with fear extinction in animals or humans or 3) examined DCS augmented with exposure therapy for clinical or nonclinical anxiety in humans. From the original pool, 29 articles were excluded from analysis. Reasons for study exclusion included the following:

1. The article was a review that did not present new data or only presented qualitative information ($n = 12$) (7,21–31).
2. The article examined the effects of DCS on something other than fear extinction, such as perception or impulsive behavior ($n = 7$) (33–39).
3. The article tested the effects of DCS after exposure to a drug of abuse ($n = 3$) (40–42).
4. The article tested DCS in conjunction with another substance ($n = 2$) (43,44).
5. Extinction training varied between PBO and DCS groups ($n = 1$) (45).
6. Sufficient information to compute effect sizes could not be obtained either from the article or from the primary author ($n = 4$) (46–49).

The 15 resultant articles yielded 30 independent samples comparing DCS versus PBO. Of the samples included in the meta-analysis, 10 included humans and 2 of them examined nonclinical participants.

Data Extraction

Data were extracted for study author, title, and year; trial design; type of subject (animal vs. human; clinical vs. nonclinical); sample size, DCS dose, and timing in relation to extinction/exposure procedures; dependent variable; and group means and SDs at post-extinction/exposure and (when available) at follow-up. Data were extracted by one of the authors and verified by another author. Table 1 shows the studies used in the present meta-analysis.

For three of the human clinical studies, multiple potential dependent measures were available. Two studies of OCD (19,20) found a significant DCS versus PBO effect after 5 sessions but not after 10. Because the timing of DCS effects in longer trials is not yet well understood, only data from the fifth session were extracted. One study of social phobia (50) employed three different standardized self-report measures of social anxiety. Because two of them are not commonly used in trials of experimental medications, only the outcomes for a measure widely used in clinical trials, the Liebowitz Social Anxiety Scale (51), were retained. These choices might increase the likelihood of Type I error by inflating the effect size for clinical samples; however, given the relative novelty of DCS augmentation and the exploratory nature of the present analysis, it was felt that this risk was preferable to the possibility of missing a clinically meaningful effect.

Data Synthesis

Data were analyzed with Comprehensive Meta-Analysis v.2.2 software. For each comparison of a DCS versus PBO sample, we calculated Cohen's *d*. A *d* value of .0 indicates no difference between DCS and PBO participants; conventionally, .2, .5, and .8 are taken to represent small, medium, and large effects, respectively (52). We also calculated the 95% confidence interval (CI), statistical significance (*p*), and within-group heterogeneity (Q_{within}) for each effect size estimate. Effect size estimates are considered significantly different from one another when their 95% CIs do not overlap. For additional clarification of differences between effect size estimates, we calculated the mixed-effects between-group heterogeneity ($Q_{between}$). An initial test of homogeneity of variance indicated heterogeneity across samples, Q_{within} (29) = 74.18, $p < .001$; therefore, random-effects models were used. Studies varied according to sample size (range 15–63); this creates a risk that a small, outlying sample will exert disproportionate influence over the mean effect size. To minimize this risk, we weighted effect size estimates by sample size (53). To test the so-called "file drawer effect" (the probability that unpublished null results would eliminate the obtained results), for each significant result we computed the "fail-safe N" (FSN) or the number of null results that would be needed to overturn a significant result. For the present analyses, we examined the number of studies that would make $p > .05$. Generally, if the FSN ≥ 5 times the number of studies in the analysis + 10 (FSN $\geq 5k + 10$), the obtained results are considered robust against the file drawer effect (53). In addition to more traditional measures (questionnaires and interviews), some of the human studies also used dependent variables that are atypical in clinical trials (e.g., shock expectancy ratings, skin conductance changes). To maximize consistency across studies, data for the human studies were limited to the best-available measure of subjective symptoms, such as semistructured interviews (18,19,54), standardized self-report (17,50), or when these were not available, subjective fear ratings (16,20,55). Moderator variables (dose, dose timing, number of sessions) were tested with linear regression analyses. The

Table 1. Studies Included in the Meta-Analysis

Study Name	*d* (post)	*d* (FU)	HED (mg/kg)	Dose Timing	Measure	# Sessions
Animal Studies						
Ledgerwood *et al.* (15) Study 1	1.22	—	2.42	−.25	% Time Freezing	1
Ledgerwood *et al.* (15) Study 2	3.49	.02	2.42	.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 3	1.43	—	1.61	.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 3	.54	—	.40	.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 3	.80	—	.81	.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 4	2.76	—	2.42	.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 4	1.43	—	2.42	2.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 4	.84	—	2.42	4.40	% Time Freezing	1
Ledgerwood *et al.* (15) Study 4	2.63	—	2.42	.90	% Time Freezing	1
Ledgerwood *et al.* (15) Study 5	1.26	—	1.61	.40	% Time Freezing	1
Ledgerwood *et al.* (66)	1.09	2.42	2.42	.40	% Time Freezing	1
Lee *et al.* (81)	.93	—	2.42	−.33	% Time Freezing	1
Lee *et al.* (81)	1.91	—	2.42	.00	% Time Freezing	1
Parnas *et al.* (57)	1.88	—	2.42	.40	% Time Freezing	1
Walker *et al.* (14)	1.17	—	—	−.25	% Increase Startle	1
Weber *et al.* (68) Study 1	.05	—	2.42	.43	% Time Freezing	1
Weber *et al.* (68) Study 2	1.05	—	2.42	.43	% Time Freezing	1
Weber *et al.* (68) Study 4	1.25	—	2.42	.43	% Time Freezing	1
Woods & Bouton (82)	−.50	—	2.42	−.25	Suppression ratio	1
Woods & Bouton (82)	.69	—	4.84	−.25	Suppression ratio	1
Human Nonclinical Studies						
Guastella *et al.* (55) Study 1	−.21	−.11	.83	−2.50	SUDS	1
Guastella *et al.* (55) Study 2	.00	−.43	4.58	−2.50	SUDS	1
Human Clinical Studies						
Specific phobia						
Ressler *et al.* (16)	.36	.27	.83	−3.00	SUDS	2
Ressler *et al.* (16)	.86	.47	8.33	−3.00	SUDS	2
Social phobia						
Guastella *et al.* (50)	.65	—	.83	−1.00	LSAS	4
Hofmann *et al.* (17)	.43	.80	.83	−1.00	SIAS	4
Panic Disorder						
Tolin *et al.* (18)	1.11	.86	.83	−1.00	PDSS	3
Obsessive-Compulsive Disorder						
Kushner *et al.* (20)	.89[a]	.43	2.08	−2.00	SUDS	5
Storch *et al.* (54)	−.19	−.36	4.17	−4.00	Y-BOCS	12
Wilhelm *et al.* (19)	.70[a]	.57	1.67	−1.00	Y-BOCS	5

d, Cohen's *d*; FU, follow-up; HED, human equivalent dose; SUDS, subjective units of discomfort (83); LSAS, Liebowitz Social Anxiety Scale (51); SIAS, Social Interaction Anxiety Scale (84); PDSS, Panic Disorder Severity Scale (85); Y-BOCS, Yale-Brown Obsessive-Compulsive Scale (86).

[a]Session 5 data used for post-treatment effect size.

DCS dose was standardized across studies by calculating human equivalent dose (HED) in mg/kg with formulas set by the U.S. Food and Drug Administration (56). This was done only for studies using systemic DCS administration; studies using intra-amygdala administration (14,15) were not used for dose-response analyses. Dose timing was calculated as the number of hours before the beginning of extinction/exposure that DCS was administered (negative numbers indicate that DCS was administered before the beginning of extinction/exposure; positive numbers indicate that DCS was administered after the beginning of extinction/exposure; a score of 0 indicates that DCS was administered exactly at the beginning of extinction/exposure). Number of sessions indicates the number of concurrent DCS + extinction/exposure sessions that were used. Studies in which multiple doses of DCS were given in the absence of extinction/exposure (57) were not included in this analysis.

Results

Effect sizes (Cohen's *d*) for all studies and specific subgroups are shown in Table 2. At post-treatment (Table 2), human studies were compared with studies of animals. This comparison yielded a significant difference ($Q_{between}$ = 10.18), with greater effects seen in animal studies. Both animal and human studies nevertheless were associated with significant effect sizes, with a large and robust effect in animal studies (d = 1.19) and a small (but not robust) effect in human studies (d = .42). Although within-group heterogeneity in the human studies was not statistically significant (p = .08), we wondered whether the outcomes for the two nonclinical human samples (55) might differ from those of clinical samples. This comparison yielded a significant difference ($Q_{between}$ = 8.57). The effect for the two nonclinical samples was not significant (in fact, the effect neared the small range in the opposite direction, with PBO seeming slightly superior to DCS, d = −.16). The human clinical studies showed a moderate effect (d = .60), although this effect remained lower than that of the animal studies ($Q_{between}$ = 6.61). Examining all studies together, DCS was associated with a significant overall effect size versus PBO when added to extinction/exposure. This effect was in the large range (d = .90) and is considered robust against the file-drawer effect.

Table 2. Effect Sizes and Comparisons Across Subgroups of Studies

Comparison	k	*n*	*d*	95% CI	FSN	Q_{within}	$Q_{between}$
Post-Treatment							
Animal	20	336	1.19[a]	.84–1.54	473[b]	40.09[c]	
Human	10	296	.42[c]	.11–.74	22	15.38	
Animal vs. human							10.18[a]
Human clinical	8	212	.60[a]	.33–.88	29	6.62	
Human nonclinical	2	84	−.16	−.59–.27	—	.19	
Human clinical vs. nonclinical							8.57[c]
Human clinical vs. animal							6.61[c]
All studies	30	632	.90[a]	.62–1.18	743[b]	74.18[a]	
Follow-Up							
Animal	2	36	1.20	−1.14–3.55	—	9.64[c]	
Human	10	292	.29[c]	.01–.57	5	12.10	
Animal vs. human							.58
Human clinical	8	208	.47[a]	.19–.75	13	5.28	
Human nonclinical	2	84	−.19	−.62–.24	—	.40	
Human clinical vs. nonclinical							6.42[c]
Human clinical vs. animal							.37
All studies	12	328	.40[c]	.05–.75	24	25.31[c]	

k, number of independent samples; *n*, number of participants; *d*, Cohen's *d*; CI, confidence interval; FSN, fail-safe *n*; Q_{within}, within-group homogeneity of variance; $Q_{between}$, between-group homogeneity of variance.

[a] $p < .001$.

[b] Robust against the file-drawer effect (FSN > 5k + 10).

[c] $p < .05$.

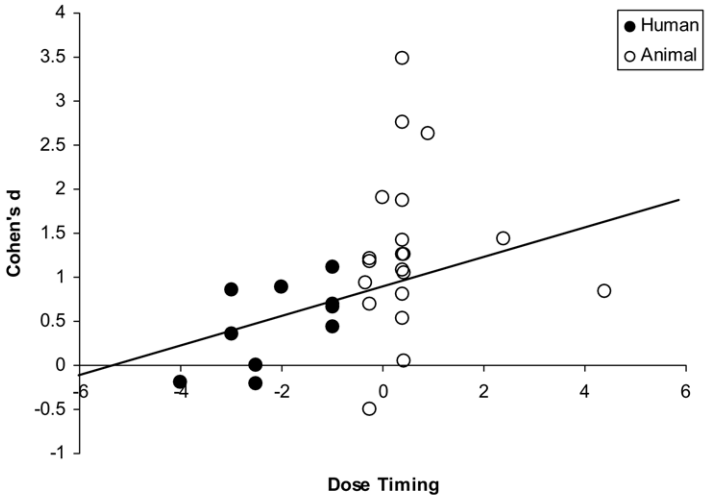
A minority of studies included follow-up data (Table 2). Animal and human studies did not differ significantly from each other ($Q_{between} = .58$). Only human studies were associated with a significant effect size ($d = .29$), although the effect size was numerically much higher for animal studies than for human studies ($d = 1.20$). As was the case for the post-treatment data, a significant difference was obtained between human clinical and nonclinical studies ($Q_{between} = 6.42$), with clinical studies showing a significant and small (although not robust) effect size ($d = .47$) and nonclinical studies showing no effect ($d = -.19$). Animal and human clinical studies did not differ significantly from each other ($Q_{between} = .37$). Across all available studies, DCS augmentation was associated with a significant and small effect size ($d = .40$), although this was not robust against the file drawer effect.

Next, we examined the effect of potential moderating variables on the effect of DCS versus PBO at post-treatment. Regression analyses (Figure 1) showed that DCS dose (HED) was not significantly associated with DCS effect ($z = .51$, $p = .61$); this was true for subgroups of animal, human clinical, and human nonclinical studies (not shown). The timing of the DCS dose significantly predicted effect size ($z = 4.53$, $p < .001$), with the greatest effects evident among studies in which DCS was administered either immediately before or after exposure/extinction. Studies in which DCS was administered multiple hours before exposure/extinction had smaller effects. Number of DCS + exposure/extinction sessions also predicted treatment outcome ($z = -2.19$, $p = .03$), with smaller effects seen for those studies in which DCS + exposure was given many times. Visual examination of Figure 1 suggests that this effect might have been the result of one outlying study (54); when this study was eliminated from analysis, there was no longer a significant relationship between treatment outcome and number of DCS + exposure sessions ($z = -.47$, $p = .64$). For additional exploration of the relationship between number of sessions and DCS effect, we examined three OCD treatment outcome studies (19,20,54) in which DCS was compared with PBO at mid- and post-treatment. As shown in Figure 2, all three studies showed a parallel decrease in DCS efficacy over time.

Discussion

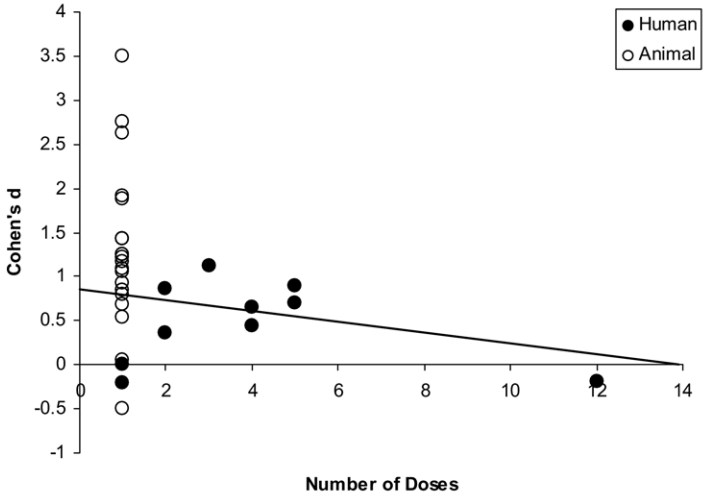
The results of the present meta-analysis suggest that DCS augments the effects of fear extinction/exposure therapy in both animals and humans. Across all samples, the effect size was large, indicating a substantial increase in efficacy. Although there is ample evidence that exposure-based treatment is effective for the treatment of anxiety disorders, many patients fail to respond adequately to treatment—for example, in studies of panic disorder, only one-half of treated patients met criteria for recovery/high end-state functioning (58,59), and many patients seek additional treatment within two years after termination (60). Although it might be expected that combining exposure-based therapy with traditional antidepressant or anxiolytic pharmacotherapy would be more effective than therapy alone, the literature to date has not supported this hypothesis. For example, recent large-scale trials for social phobia (61), OCD (62), and panic disorder (63) failed to provide compelling evidence of a long-term beneficial effect of adding antidepressant medications to exposure-based therapy; similar findings have been obtained in studies augmenting exposure-based therapy with benzodiazepines (64). Rather than an additive approach in which anxiety-reducing psychotherapy and pharmacotherapy are combined, DCS augmentation is based on an interactive model in which the pharmacotherapy systematically targets and augments the proposed neural mechanism of the psychotherapy.

Animal studies evidenced greater and more robust effects than human studies; however, this difference was attenuated when nonclinical human studies were removed from the analyses. The two nonclinical studies found no evidence of DCS augmentation in experimentally induced fear when using a differential shock paradigm (46) or when using exposure therapy for subclinical spider phobia (55). These results might be explained by a ceiling effect: 100% of the subclinical spider



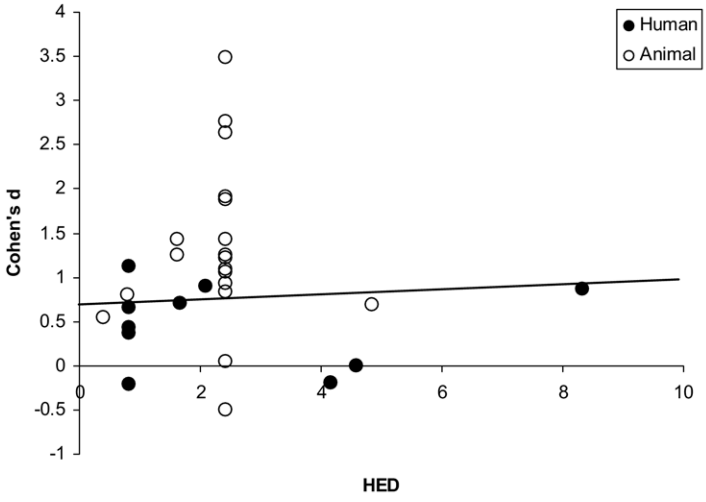
Dose timing from beginning of extinction/exposure

$z = 4.53, p < .001$



Number of DCS + exposure/extinction sessions

$z = -2.19, p = 0.03$



Dose (HED, mg/kg)

$z = 0.51, p = 0.61$

Figure 1. Regressions of moderator variables against effect size. DCS, D-cycloserine; HED, human equivalent dose.

fearful participants completed all behavioral assignments over a 2-hour exposure session, which included handling large spiders that can produce painful bites (55). Typically, healthy participants or mildly phobic individuals do not require extensive extinction training to return to preconditioning levels.

A greater effect in animal studies is perhaps not surprising, given the greater experimental control over extraneous variables

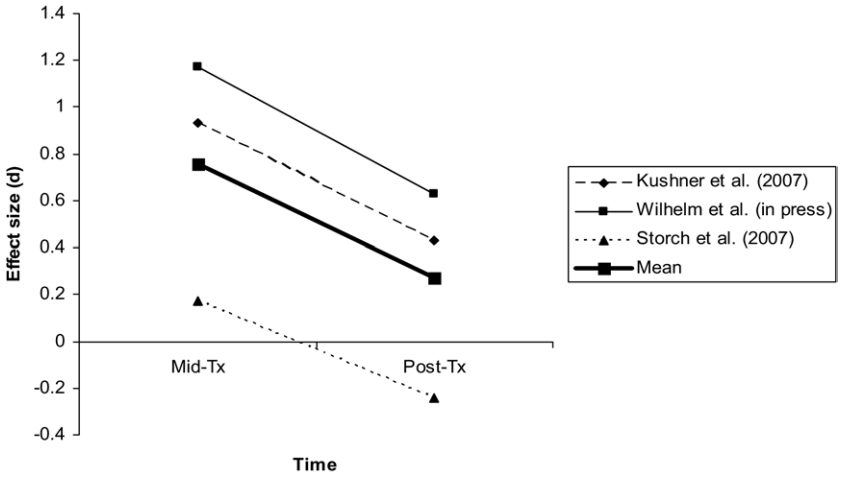


Figure 2. Effect sizes at mid- (Mid-Tx) and post-treatment (Post-Tx) for three studies of D-cycloserine augmentation of behavior therapy for obsessive-compulsive disorder.

in animal studies. In animal studies, subjects only receive extinction training in the presence or absence of DCS, whereas human patients are able to expose themselves to their feared situations outside of the therapeutic context. In addition, research animals are highly inbred, and thus results would be expected to be less variable.

Also noteworthy, the human studies were not robust against the "file drawer" effect, likely owing to the relatively small number and sample sizes of existing studies (e.g., 8 human clinical studies with $n = 84$, compared with 20 animal studies with $n = 336$). Nevertheless, the generally comparable findings across animal and human studies suggest that DCS is a promising tool for translational research concerned with enhancing (or reducing) NMDA receptor function as a method for improving exposure-based therapy outcomes.

Relatively few studies have examined the long-term effects of DCS on fear extinction/exposure therapy, although the existing studies show significant and moderate effect sizes at follow-up. When analyzing animal and human studies separately, only human studies were associated with a significant effect size at follow-up. This finding is likely due to the small number of animal samples that provided follow-up data, as the effect size for animal studies was numerically higher than human studies. Similar to post-treatment data, nonclinical human studies were not associated with a significant effect of DCS at follow-up. These preliminary results suggest that the effects of DCS augmentation do not disappear upon treatment discontinuation, a potential improvement over other pharmacotherapy augmentation strategies that might actually increase the risk of relapse after discontinuation (63,64).

The present results indicate that the augmenting effect of DCS is potentially dependent on the timing and number of doses. These factors are perhaps best illustrated by Storch *et al.* (54), who did not find a positive effect of DCS versus PBO. Unlike the two other OCD trials (19,20), Storch *et al.* administered DCS for a longer period of time (12 weeks vs. 5 weeks) and used a longer duration between administration and initiation of an exposure session (4 hours vs. 1–2 hours). Figure 1 clearly shows the Storch *et al.* study as an outlier in terms of these two variables. When this study was removed from analysis, the number of DCS augmented fear extinction/exposure therapy sessions was not related significantly to outcome; however, when the study was included in the analysis, smaller effects were seen for those studies that used a greater number of sessions. The finding that the number of sessions was related negatively to outcome is tentative, because two of the effect sizes used for the human studies (both samples of OCD patients) were selected post hoc from time points when a separation occurred from DCS and PBO (19,20). Given the number of uncertainties in DCS research, the mid-treatment time point was used so that potential differences between DCS and PBO would not be missed; however, across all three OCD studies, the effect of DCS decreased over repeated sessions. This decrease might be the result of desensitization to DCS (57) or it might reflect floor effects of repeated exposures (i.e., with enough exposure therapy there might be little need for augmentation). This suggests that DCS's major contribution to exposure-based therapy might be to increase its speed or efficiency. Consistent with this suggestion, Ledgerwood *et al.* (65) have demonstrated in animals that DCS can block the reinstatement of previously extinguished fear and that its effects can generalize to non-extinguished conditioned stimuli (66). Increasing the speed of treatment is a worthwhile pursuit, because it might be expected to lead to reduced attrition, increased satisfaction, decreased treatment cost, increased ease of dissemination to primary care, and decreased economic burden of illness.

The finding that DCS is most effective when administered immediately before or after fear extinction/exposure therapy suggests that the augmenting effects of DCS take place during the period of memory consolidation that occurs after training. Animal studies using NMDA receptor antagonists at various intervals after extinction training suggest that NMDA-dependent fear extinction occurs in waves lasting 1–2 days after training, as hippocampal-neocortical synaptic connections are strengthened (67). Because DCS reaches peak plasma levels 4–8 hours after oral administration, drug levels would be expected to be highest during the period of post-session memory consolidation if administered after a fear extinction/exposure therapy session. Another potential benefit of administering DCS immediately after fear extinction/exposure therapy sessions is the possibility for the clinician to administer DCS only after sessions in which within-session extinction has occurred. This procedure would be consistent with animal research showing that DCS leads to long-term gains only for animals exhibiting within-session extinction (68). Such selective administration would also lessen the possibility of tolerance due to chronic administration, as described in the preceding text.

The DCS dose was not significantly associated with DCS effect in any subgroup. This null finding should be considered tentative, because only two studies to date have compared multiple

doses within a single study. Ledgerwood *et al.* (15) found effects of .54, .80, and 1.43 for DCS versus PBO in rats with 2.5 mg, 5 mg, and 10 mg, respectively, whereas Ressler *et al.* (16) found effects of .36 and .86 for DCS versus PBO in phobic humans with 50 mg and 500 mg, respectively. In both of these studies a pattern of greater effects was evidenced at higher doses.

The beneficial effects of DCS in anxiety disorders contrast with findings from the use of DCS as a corrective treatment for neurocognitive deficits in schizophrenia and Alzheimer's disease (69,70). Despite early promising results (71–73), larger and more recent trials (74–76) yielded generally nonsignificant findings relative to PBO (70,77). In the treatment of schizophrenia and Alzheimer's disease, D-cycloserine has been applied in chronic daily doses, unlike the extinction-augmenting applications used in treatments of conditioned fear. As shown by the present results, isolated dosing might be more effective than chronic dosing for specific learning-based purposes, consistent with the demonstration of desensitization of the NMDA receptor complex in cell culture with prolonged exposure to DCS and other glycinergic ligands (78).

Many questions remain unanswered concerning the usefulness of DCS augmented exposure therapy. For example, additional dose-finding research in animals and humans is needed to clarify how DCS might interact with other common psychiatric medications. We excluded, as noted previously, two animal studies in which DCS was administered concurrently with other medications (43,44). Yet, many of the human clinical studies included patients that received concurrent pharmacotherapy. Thus, it might initially seem that the inclusion criteria for the meta-analysis differed across human and animal studies; however, the retained human clinical studies required a period of medication stability that allows for a more definitive examination of the effects of DCS, unlike the two animal studies that were excluded. One animal study (79) found that rats pre-exposed to imipramine over 14 days showed reduced DCS facilitation of extinction training. Human trials of DCS administered along with antidepressant and benzodiazepine medications would clarify this issue for clinical practice.

Another direction for future research is to examine whether DCS is effective for individuals who have not successfully responded to prior trials of exposure-based monotherapy. Such application would likely reflect typical clinical practice, in which novel or "off label" compounds are administered after the failure of more conventional treatments. To the extent that treatment failure is due to inadequate within- or between-session extinction, DCS augmentation might be expected to enhance outcomes.

In addition, DCS needs to be examined in the treatment of a broader range of anxiety-related conditions. Early studies (16,29) treated phobic disorders that are fairly homogeneous and whose treatment is easily standardized. Recent results with chronic and heterogeneous conditions such as OCD (19,20,54) have been more mixed but overall seem consistent with the previous findings. Additional research with conditions such as posttraumatic stress disorder, also treated with exposure-based interventions (80), would help clarify the range of DCS applicability.

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