D-Cycloserine Augmentation of Behavioral Therapy for the Treatment of Anxiety Disorders: A Meta-Analysis

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ABSTRACT

Objective: To determine the efficacy of D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders.

Data Sources and Study Selection: Using the search terms *D-cycloserine* AND *anxiety disorders* (MeSH), PubMed (1965–June 2011), PsycINFO, and Scopus were searched for randomized, double-blind, placebo-controlled trials of D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders. Anxiety disorders were defined as any disorder categorized as such in *DSM-IV-TR*.

Data Extraction: A random-effects model was used to calculate the standardized mean difference of change in anxiety rating scale scores with D-cycloserine augmentation compared to placebo, which was the primary outcome measure. Subgroup analysis and meta-regression were used to examine the effects of D-cycloserine dosage and timing (relative to exposure therapy), diagnostic indication, number of therapy sessions, and trial methodological quality on D-cycloserine efficacy.

Results: Meta-analysis of 9 trials involving 273 subjects demonstrated a significant benefit from D-cycloserine augmentation (standardized mean difference = 0.46 [95% CI, 0.15 to 0.77], $z = 2.89$, $P = .004$). There was no evidence of publication bias, but a moderate, nonsignificant degree of heterogeneity between trials ($I^2 = 36\%$, $Q = 12.6$, $df = 8$, $P = .12$) was found. Secondary analyses yielded no significant findings.

Conclusions: D-Cycloserine appears to be an effective augmentation agent that enhances the effects of behavioral therapy in the treatment of anxiety disorders. In contrast to a previous meta-analysis that examined D-cycloserine's effects in both animals and humans, we found no evidence of an effect of dose number, dose timing, or dosage of D-cycloserine on reported efficacy in the ranges studied.

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Anxiety disorders are the most prevalent class of psychiatric disorders, affecting nearly 20% of the population.[1,2] Anxiety disorders impair quality of life, including the social and occupational functioning of patients who suffer from them.[2,3] Cognitive-behavioral therapy (CBT) is a first-line treatment for all anxiety disorders including specific phobia, social phobia, panic disorder, and obsessive-compulsive disorder (OCD). A meta-analysis[4] of randomized, controlled trials of CBT for anxiety disorders demonstrated that CBT has large treatment effects, with subjects receiving CBT being 4-fold more likely to respond to treatment compared to those receiving placebo. Treatment effects for CBT were greatest for OCD (effect size [ES] = 1.4) and acute stress disorder (ES = 1.3) and lowest for generalized anxiety disorder (ES = 0.5) and panic disorder (ES = 0.4).[4] Despite the clear evidence of efficacy for CBT in the treatment of anxiety disorders, many patients do not respond to this treatment. Furthermore, 5%–20% of subjects receiving CBT in randomized, controlled trials drop out of treatment.[5] Although the numbers of dropouts in CBT trials are typically smaller than in pharmacologic trials for anxiety disorders, early discontinuation of CBT still represents a substantial barrier to treatment. Lastly, CBT, even when effective, requires several sessions and typically several months to achieve maximum efficacy. Therefore, substantial need to improve the efficacy, speed, and tolerability of CBT remains.

D-Cycloserine is a pharmacologic agent that has been demonstrated to enhance the function of the *N*-methyl-D-aspartate glutamate receptor by stimulating its high-affinity glycine binding site.[6] Animal trials have consistently demonstrated that D-cycloserine can enhance the process of fear extinction in animals.[7] Fear extinction is a particular learning process whereby new associations can be formed to compete with fearful ones by presenting the conditioned stimulus in the absence of the unconditioned stimulus.[8,9] Given the similarity between fear extinction training in animals and the learning that takes place during the practice of exposure-based behavioral therapy in the treatment of anxiety disorders in humans, it was hypothesized that D-cycloserine might be a translational agent able to enhance the efficacy of CBT in humans.

Several double-blind, randomized, placebo-controlled trials have assessed the efficacy of augmenting behavioral therapy with D-cycloserine. A comprehensive meta-analysis[7] examined the efficacy of D-cycloserine in enhancing fear extinction learning in both animal and human trials. This meta-analysis demonstrated significant efficacy of D-cycloserine augmentation in human studies with an attenuated but still significant effect maintained at follow-up. Moderator analysis examining both animal and human studies analyzed together found that D-cycloserine augmentation was most effective when D-cycloserine was given at a time more proximal to the time of exposure and that the efficacy of D-cycloserine augmentation may diminish with increasing number of doses.[7] These findings, if accurate, have important implications for the clinical use of D-cycloserine in humans. However, the findings may be the result of confounding rather than true attributes of D-cycloserine augmentation.[7] In animal studies, compared with human studies, (1) greater effects of D-cycloserine augmentation were seen and (2) D-cycloserine tended to be dosed fewer times and closer to the time of exposure.[7]

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To best generalize research results to clinical practice and to eliminate the possibility of confounding effects by the greater efficacy of D-cycloserine augmentation in animal studies, we restricted our examination to trials involving humans with anxiety disorders. The goal of this meta-analysis was to determine the efficacy of double-blind, randomized, placebo-controlled trials of D-cycloserine augmentation of CBT for anxiety disorders. We focused specifically on moderators of treatment effect to determine if the efficacy of D-cycloserine augmentation varied by (1) type of anxiety disorder, (2) dosage or timing of D-cycloserine, and (3) length of CBT.

Clinical Points

- D-Cycloserine appears to enhance the effects of cognitive-behavioral therapy for anxiety disorders.
- In contrast to a previous meta-analysis that combined results of animal and human studies, we found no significant effect of dose timing or number of doses on the efficacy of D-cycloserine.
- Further trials are needed to clarify how the efficacy of D-cycloserine may differ between anxiety disorders and with prolonged use.

METHOD

Search Strategy

All meta-analytic methods and sensitivity analyses were specified prior to conducting the meta-analysis but were not registered online. PubMed (1965–June 2011), PsycINFO, and Scopus were searched by 2 reviewers (A.B. and K.E.P.) for relevant citations using the search terms *D-cycloserine* AND *anxiety disorders* (MeSH). The PubMed search was further limited using the randomized controlled trial and meta-analysis filters. The bibliographies of related review articles, meta-analyses, and included articles were also searched for additional eligible citations. Authors of some articles were contacted for missing information when necessary. There were no limitations based on the language of publication.

Inclusion Criteria

Trials were included in our meta-analysis if they were randomized, placebo-controlled trials assessing the efficacy of D-cycloserine augmentation of behavioral therapy in the treatment of anxiety disorders (as defined by *DSM-IV-TR*). Trials were not included if they were conducted on animals or if they were conducted in a human population without a diagnosed anxiety disorder. Randomized controlled trials were identified if the investigator defined them as such in the methods section of the article.

Meta-Analytic Procedure

To extract data from included articles, we used Excel spreadsheets (version 14.1.4; Microsoft; Redmond, Washington). Data extracted included timing and dose of D-cycloserine, diagnostic indication, duration of behavioral therapy (in number of sessions), method of analysis (intention-to-treat vs completers), ratings of trial quality using the Jadad scale,[10] sample size, number of dropouts, and age of sample (children vs adults). Missing information was requested from study investigators.

Our primary outcome measure was mean improvement in the primary rating scale scores used to measure anxiety in the trial. We examined the difference between D-cycloserine and placebo by calculating the standardized mean difference (SMD) using Comprehensive Meta-Analysis (Biostat; Englewood, New Jersey). This measure was favored over weighted mean difference, because rating scales differed between the included studies. A random-effects (as opposed to fixed-effects) model was used for the meta-analysis because there was considerable evidence of heterogeneity between trials.

Publication bias was assessed by plotting the effect size against standard error for each trial (funnel plot).[11] In addition, publication bias was statistically tested by the Egger test and by determining the association between sample size and effect size in meta-regression.[11] Heterogeneity between trials was determined by means of 2 separate statistical estimates using Comprehensive Meta-Analysis. First, a Q-statistic was employed to provide a test of statistical significance indicating whether the differences in effect sizes are due to subject-level sampling error alone or other sources. In addition, we estimated heterogeneity using the I^2 statistic, which estimates the proportion of total variance that is attributable to between-study variance.

For secondary analyses, we performed several subgroup analyses and meta-regression. Stratified subgroup analysis in Comprehensive Meta-Analysis was used to assess the effects of (1) diagnostic indication (OCD, social phobia, panic disorder, or other anxiety disorder) and (2) method of analysis (completers vs intention-to-treat). We used the test for subgroup differences in Comprehensive Meta-Analysis to determine whether subgroups reduced overall heterogeneity.[12] We initially intended to examine the effects of age group (child vs adult) on the effects of D-cycloserine. However, there were not enough trials in children to conduct this analysis.

Meta-regression was performed in Comprehensive Meta-Analysis Version 2. To examine the association between D-cycloserine efficacy in trials and continuous variables such as (1) dose, (2) timing of D-cycloserine dosage (in hours before treatment), (3) number of doses of D-cycloserine given, (4) therapy sessions, (5) number of exposure-based therapy sessions, (6) proportion of therapy sessions that were exposure-based, (7) trial methodological quality, and (8) sample size, we used a meta-regression technique. For meta-regression, effect size was the dependent variable and our variable of interest was the independent variable. Studies were weighted using the generic inverse variance method. Our threshold for statistical significance was selected to be $P < .05$ for the primary analysis, as well as for all subgroup analyses and meta-regression. Any significant findings in secondary analyses should be regarded as exploratory because

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Figure 1. Selection of Studies: Meta-Analysis of D-Cycloserine Augmentation of Behavioral Therapy in the Treatment of Anxiety Disorders

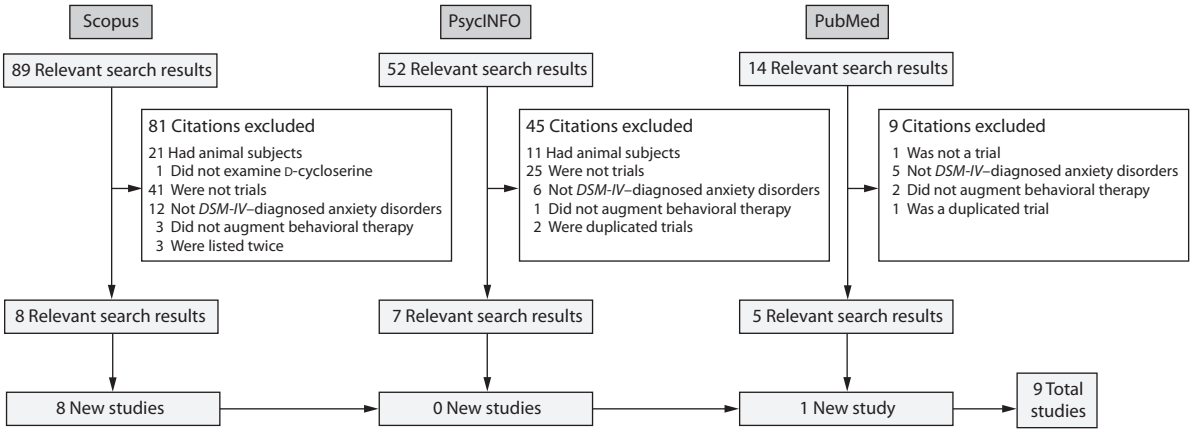

Table 1. Characteristics of Trials Included in a Meta-Analysis of D-Cycloserine (DCS) Augmentation of Behavioral Therapy in the Treatment of Anxiety Disorders

Study	Diagnosis	DCS Dose (mg)	Timing of DCS Dosing (h)[a]	No. of DCS Doses	Therapy	No. of Exposure Sessions	Total No. of Therapy Sessions	N	Age	Analysis	Primary Outcome
Ressler et al, 2004[13]	Acrophobia	275	3	2	Virtual reality exposure	2	2	27	Adult	ITT	Subjective units of discomfort
Hofmann et al, 2006[3]	SAD	50	1	4	Exposure	4	5	27	Adult	Completer	SPAI
Storch et al, 2007[8]	OCD	250	4	12	Exposure and response prevention	10	12	24	Adult	Completer	YBOCS
Kushner et al, 2007[14]	OCD	125	2	4	Exposure and response prevention	4	4	25	Adult	ITT	YBOCS
Guastella et al, 2008[15]	SAD	50	1	4	Exposure	4	5	50	Adult	ITT	SPAI
Wilhelm et al, 2008[16]	OCD	100	1	10	Exposure	10	10	23	Adult	ITT	YBOCS
Otto et al, 2009[17]	Panic disorder	50	1	3	CBT	4	5	28	Adult	Completer	PDSS
Storch et al, 2010[18]	OCD	50	1	7	CBT	7	10	30	Child	ITT	CYBOCS
Siegmund et al, 2011[19]	Panic disorder	50	1	3	CBT	3	11	39	Adult	Completer	PAS

[a]Length of time from D-cycloserine dosing until behavioral therapy.
Abbreviations: CBT = cognitive-behavioral therapy, CYBOCS = Children's Yale-Brown Obsessive Compulsive Scale, ITT = intention-to-treat, PAS = Panic and Agoraphobia Scale, PDSS = Panic Disorder Severity Scale, SAD = social anxiety disorder, SPAI = Social Phobia and Anxiety Inventory, YBOCS = Yale-Brown Obsessive Compulsive Scale.

we did not adjust for inflation of false-positive error from our 8 secondary analyses.

RESULTS

Included Studies

We included 9 studies with a total of 273 subjects in this meta-analysis.[3,8,13–19] Figure 1 is a flowchart presenting the selection of these 9 trials from a total of 155 identified publications. Four of the studies examined the efficacy of D-cycloserine for the treatment of OCD.[8,14,16,18] Two studies each examined the efficacy of D-cycloserine for social phobia[3,15] and panic disorder.[17,19] One study examined D-cycloserine for acrophobia.[13] Table 1 depicts the characteristics of included studies in this meta-analysis.

Efficacy of D-Cycloserine Augmentation

D-Cycloserine augmentation demonstrated a significant effect in enhancing the benefits of behavioral therapy for anxiety disorders (SMD = 0.46 [95% CI, 0.15 to 0.77], $z = 2.89$, $P = .004$). Figure 2 illustrates a forest plot depicting the estimated efficacy of D-cycloserine from individual trials.

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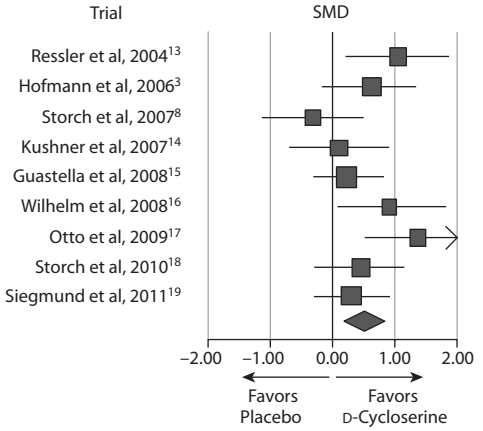
There was some evidence of heterogeneity between trials (I^2 = 36%, Q = 12.6, df = 8, P = .12). The Egger test (P = .20) and a meta-regression of effect size vs sample size (β = −0.02 [95% CI, −0.06 to 0.02], z = −0.93, P = .35) indicated no evidence of publication bias. When a fixed-effects rather than random-effects model was used for the meta-analysis, the findings were similar (SMD = 0.44 [95% CI, 0.19 to 0.68], z = 3.49, P < .001).

Diagnostic Indication

Subgroup analysis demonstrated no significant effect of diagnostic indication on the efficacy of D-cycloserine augmentation of behavioral therapy (test for subgroup differences, χ^2_3 = 3.55, P = .31). The 4 trials studying D-cycloserine in the treatment of OCD (SMD = 0.25 [95% CI, −0.15 to 0.64], z = 1.23, P = .22) and the 2 trials examining social phobia (SMD = 0.35 [95% CI, −0.11 to 0.80], z = 1.51, P = .13) reported smaller effects of D-cycloserine than trials of acrophobia (SMD = 1.01 [95% CI, 0.19 to 1.84], z = 2.40, P = .02) and panic disorder (SMD = 0.65 [95% CI, 0.14 to 1.16], z = 2.48, P = .01). However, this difference did not approach statistical significance.

Figure 2. Efficacy of D-Cycloserine Augmentation of Behavioral Therapy in the Treatment of Anxiety Disorders[a]



[a]D-Cycloserine augmentation demonstrated a significant benefit for treating anxiety disorders (SMD = 0.46 [95% CI, 0.15–0.77], z = 2.89, P = .004). There was modest, although not statistically significant, evidence of heterogeneity between trials (I^2 = 36%, Q = 12.6, df = 8, P = .12).
Abbreviation: SMD = standardized mean difference.

Dose of D-Cycloserine

Meta-regression demonstrated no significant effect of D-cycloserine dosage (within the 50–500 mg range) on efficacy of D-cycloserine augmentation (β = −0.0006 [95% CI, −0.0037 to 0.0024], z = −0.41, P = .68, R^2 < .01).

Timing of D-Cycloserine Dose

Included trials dosed D-cycloserine 1–4 hours prior to behavioral therapy sessions. Meta-regression demonstrated no significant effect of timing of D-cycloserine dosing prior to treatment on measured efficacy (β = −0.15 [95% CI, −0.40 to 0.10], z = −1.20, P = .23, R^2 = .11).

Duration of D-Cycloserine Augmentation

Included trials augmented behavioral therapy with D-cycloserine for 2–12 treatment sessions. Meta-regression found no association between the number of doses and the efficacy of D-cycloserine augmentation (β = −0.056 [95% CI, −0.138 to 0.025], z = −1.36, P = .17, R^2 = .15).

Characteristics of Therapy

Meta-regression found no association between the total number of therapy sessions (β = −0.054 [95% CI, −0.128 to 0.019], z = −1.44, P = .15, R^2 = .16), the number of exposure-based sessions (β = −0.044 [95% CI, −0.140 to 0.050], z = −0.92, P = .36, R^2 = .07), or the proportion of therapy sessions that were exposure based (β = 0.1 [95% CI, −0.9 to 1.2], z = −0.24, P = .81, R^2 < .01) and the reported efficacy of D-cycloserine augmentation.

Methodological Quality of Trial

Meta-regression demonstrated no significant effect of trial methodological quality on efficacy of D-cycloserine augmentation between trials (β = −0.20 [95% CI, −0.50 to 0.09], z = −1.34, P = .18, R^2 = .14).

Method of Analysis

Subgroup analysis showed no difference based on method of analysis (test for subgroup differences, χ^2_1 = 0.01, P = .93). Trials analyzed using just completers' data (SMD = 0.43 [95% CI, 0.11 to 0.75], z = 2.65, P = .01) reported similar effects compared to trials employing an intention-to-treat analysis (SMD = 0.45 [95% CI, 0.06 to 0.84], z = 2.27, P = .02).

DISCUSSION

This meta-analysis demonstrated significant efficacy for the use of D-cycloserine to augment behavioral therapy in the treatment of anxiety disorders. There was a large amount of heterogeneity between trials, but secondary subgroup analyses and meta-regression did not explain the sources of heterogeneity. In contrast to a previous meta-analysis,[7] which examined the effects of D-cycloserine in both animals and humans, we demonstrated no significant effect of dose timing or number of doses on treatment efficacy. We believe that our findings differ from the results of the previous meta-analysis because our meta-analysis examined only humans. It appears as though the results of the previous meta-analysis can be attributed to confounding effects. For example, animal studies administered D-cycloserine following exposure sessions and found a greater effect of D-cycloserine augmentation. On the other hand, in the studies of humans, D-cycloserine was administered several hours before exposure and showed a lesser effect of D-cycloserine augmentation.[7] The previous

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meta-analysis also found that D-cycloserine worked more effectively when utilized for a limited number of sessions.[7] Animal trials typically administered D-cycloserine for only 1 session, whereas human studies often administered it during multiple sessions. Another possibility for the differing results between these 2 meta-analyses is the increased statistical power in the previous meta-analysis, which also included animal studies (which outnumber human studies 2-fold). Evidence arguing against this possibility is that the size of the moderating effect of duration of treatment was roughly 25% smaller in our analysis compared to the previous meta-analysis. The moderating effect of D-cycloserine dose timing reported in our study was in the opposite direction of the effect seen in the previous meta-analysis that included both animal and human studies. The lack of significant association between the efficacy of D-cycloserine augmentation and the number of sessions may have important clinical implications. Our finding suggests that D-cycloserine may still have significant effects in improving outcome in patients treated with CBT for anxiety disorders for longer durations.

Taking these findings into consideration, it is important to highlight some of the limitations of this meta-analysis. For example, there were a limited number of trials included in this meta-analysis. The relatively small number of trials limited our ability to detect potential moderators of treatment effect (such as dose, duration of treatment, and type of anxiety disorder). Also, the relatively limited range of D-cycloserine dose timing may have limited our ability to detect the effects of this moderating variable. Finally, potential moderator variables are often correlated in studies (eg, OCD behavioral therapy trials are usually of longer duration). The relatively small number of studies in this area precludes us from conducting multivariate models that would allow us to assess the effects of moderator variables more independently. Additional trials would allow us to provide a more precise estimate of the treatment effects of D-cycloserine and allow us to take a more comprehensive look at sources of heterogeneity between trial results. We hypothesize that (1) methodological differences in behavioral techniques in trials (ie, strict use of exposure therapy/fear-extinction learning versus the incorporation of additional cognitive components) and (2) particular type of anxiety disorder may be particularly important causes of heterogeneity between trials and therefore deserve further research.

Despite these limitations, this meta-analysis demonstrates that D-cycloserine is an effective augmentation agent to enhance the effects of behavioral therapy for anxiety disorders. Subgroup analyses suggest that D-cycloserine augmentation may be more effective for panic disorder or specific phobias than for treating OCD and social phobia. Further research is needed to examine moderators of D-cycloserine treatment effects—particularly, type of anxiety disorder (and therapy) and the interaction of the effect of D-cycloserine with time of treatment.

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