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

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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—We searched PubMED, PsycINFO and Scopus 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—We used a random effects model to calculate the standardized mean difference of change in anxiety rating scales of D-cycloserine augmentation compared to placebo, which was our primary outcome measure. We used subgroup analysis and meta-regression to examine the effects of D-cycloserine timing and dosage, diagnostic indication, number of therapy sessions and trial methodological quality on D-cycloserine efficacy.

Results—Meta-analysis of nine trials involving 273 subjects demonstrated a significant benefit from D-cycloserine augmentation (SMD=0.46 (95% CI: 0.15–0.77), z=2.89, p=0.004). There was no evidence of publication bias but a moderate, non-significant degree of heterogeneity between trials (I^2=36%, Q=12.6, df=8, p=0.12). 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 and dosage of D-cycloserine on reported efficacy in the ranges studied.

Keywords

D-cycloserine; Anxiety Disorders; Behavioral Therapy; Meta-Analysis

INTRODUCTION

Anxiety disorders are the most prevalent class of psychiatric disorders affecting nearly 20% of the population.[1,2] Anxiety disorders impair the quality of life including the social and occupational functioning of patients who suffer from them.[3,2] 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 of randomized, controlled trials of CBT for anxiety disorders has demonstrated that CBT has

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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 (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 number of dropouts in CBT trials is typically smaller than that in pharmacological trials for anxiety disorders, this still represents a substantial barrier to treatment. Lastly, CBT, even when effective, requires several sessions and typically several months to achieve maximum efficacy. Therefore, there remains substantial need to improve the efficacy, speed and tolerability of CBT.

D-cycloserine is a pharmacological agent that has been demonstrated to enhance NMDA glutamate receptor function 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 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 recently examined the efficacy of D-cycloserine in enhancing fear extinction learning in both animal and human trials.[7] This meta-analysis demonstrated significant efficacy of D-cycloserine augmentation in human studies with an attenuated but still significant effect maintained at follow-up.[7] Moderator analysis examining both animal and human studies treated together found that D-cycloserine augmentation was most effective when D-cycloserine was given more proximal to the time of exposure and that the efficacy of D-cycloserine augmentation may diminish with increasing number doses.[7] These findings, if accurate, have important implications for the clinical use of D-cycloserine in humans. However, these findings may be the result of confounding rather than true attributes of D-cycloserine augmentation.[7] Animal studies (1) showed greater effects of D-cycloserine augmentation than human studies and (2) D-cycloserine tended to be dosed fewer times and closer to the time of exposure in animal studies.[7]

In order 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 specifically focused 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.

METHODS

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 two reviewers (AB and KEP) for relevant citations using the search terms “(D-cycloserine and Anxiety Disorders (MeSH).” Our search in PubMED was

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further limited using the randomized controlled trial and meta-analysis filters. The bibliography 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. 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 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, NJ). This measure was favored over weighted mean difference, because rating scales differed between the included studies. A random (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's test and by determining the association between sample size and effect size in meta-regression.[11] Heterogeneity between trials was determined by means of two 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 *I-square* 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 D-cycloserine's effects. 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

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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 subgroups analyses and meta-regression. Any significant findings in secondary analyses should be regarded as exploratory because we did not adjust for inflation of false-positive error from our 8 secondary analyses.

RESULTS

Included Studies

We included nine studies with a total of 273 subjects in this meta-analysis.[3,8,13,14–19] Figure 1 is a flow chart presenting the selection of these nine trials from a total of 161 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: 0.15–0.77), z=2.89, p=0.004). Figure 2 illustrates a forest plot depicting the estimated efficacy of D-cycloserine from individual trials. There was some evidence of heterogeneity between trials (I^2=36%, Q=12.6, df=8, p=0.12). The Egger's test (p=0.20) and a meta-regression of effect size vs. sample size (β=−0.02 (95% CI: −0.06- 0.02), z=−0.93, p=0.35) 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: 0.19–0.68), z=3.49, p<0.001).

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=3.55, df=3, p=0.31). The four trials studying D-cycloserine in the treatment of OCD (SMD=0.25 (95%CI: −0.15–0.64), z=1.23, p=0.22) and the two trials examining social phobia (SMD=0.35 (95%CI: −0.11–0.80), z=1.51, p=0.13) reported smaller effects of D-cycloserine than trials of acrophobia (SMD=1.01 (95%CI: 0.19–1.84), z=2.40, p=0.02) and panic disorder (SMD=0.65 (95%CI: 0.14–1.16), z=2.48, p=0.01). However, this difference did not approach statistical significance.

Dose of D-cycloserine

Meta-regression demonstrated no significant effect of D-cycloserine dosage (within the 50–500mg range) on efficacy of D-cycloserine augmentation (β=−0.0006 (95% CI: −0.0037-0.0024), z=−0.41, p=0.68, R^2<0.01).

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- 0.10), z=-1.20, p=0.23, R^2=0.11).

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Duration of D-cycloserine Augmentation

Included trials augmented behavioral therapy with D-cycloserine for 2–11 treatment sessions. Meta-regression found no association between the number of doses and the efficacy of D-cycloserine augmentation (β=−0.056 (95% CI: −0.138-0.025), z=−1.36, p=0.17, R^2=0.15).

Characteristics of Therapy

Meta-regression found no association between the total number of therapy sessions (β=−0.054 (95% CI: −0.128-0.019), z=−1.44, p=0.15, R^2=0.16), the number of exposure-based sessions (β=−0.044 (95% CI: −0.140-0.050), z=−0.92, p=0.36, R^2=0.07) or the proportion of therapy sessions that were exposure based (β=0.1 (95% CI: −0.9–1.2), z=−0.24, p=0.81, R^2<0.01) 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: −0.50-0.09), z=−1.34, p=0.18, R^2=0.14).

Method of Analysis

Subgroup analysis showed no difference based on method of analysis (Test for subgroup differences χ^2=0.01, df=1, p=0.93). Trials analyzed using just completers' data (SMD=0.43 (95%CI: 0.11–0.75), z=2.65, p=0.01) reported similar effects compared to trials employing an intention-to-treat analysis (SMD=0.45 (95%CI: 0.06–0.84), z=2.27, p=0.02).

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, 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. [7] We believe that our findings differ from the results of the previous meta-analysis because the previous meta-analysis included both human and animal trials, while this meta-analysis only examined 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 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 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 one session, whereas human studies often administered it during multiple sessions. Another possibility for the differing results between these two meta-analyses is the increased statistical power in the previous meta-analysis, which also included animal studies (which outnumber human studies two-fold). Evidence arguing against this possibility is that the size of the moderating effect of duration of treatment was roughly 25% smaller compared to the previous meta-analysis. Our reported moderating effect of D-cycloserine dose timing was in the opposite direction of 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 significant clinical implications. Our finding suggests that D-

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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 few 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 DCS dose timing may have limited our ability to detect the effects of this moderating variable. Finally, potential moderator variables are often correlated in studies (e.g. OCD behavioral therapy trials are usually of longer duration). The relatively small numbers 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 D-cycloserine's treatment effects and allow us to take a more comprehensive look at sources of heterogeneity between trial results. We would hypothesize that (1) methodological differences in behavioral techniques in trials (i.e. 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 that 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 D-cycloserine's effect with time of treatment.

CLINICAL POINTS

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

PODCAST

D-cycloserine is a pharmacological agent that has been demonstrated to enhance NMDA glutamate receptor function by stimulating its high-affinity glycine binding site. D-cycloserine has been demonstrated to enhance the process of fear extinction in animals. Several investigators have conducted double-blind, placebo-controlled trials to assess the efficacy of D-cycloserine in enhancing the effects of cognitive behavioral therapy of anxiety disorders. We conducted a meta-analysis to determine the efficacy of D-cycloserine as augmentation of behavioral therapy for the treatment of anxiety disorders in humans. This meta-analysis of nine trials involving 273 subjects demonstrated a significant benefit from D-cycloserine augmentation. This benefit was of moderate effect size. We found no moderating effect of D-cycloserine dosage, dose timing, or dose number on D-cycloserine's reported efficacy. The underlying anxiety disorder being treated also did not significantly influence D-cycloserine's efficacy. Further research is needed to further examine moderators

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of D-cycloserine treatment effects – particularly, type of anxiety disorder (and therapy) and the interaction of D-cycloserine's effect with duration of treatment.

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Abbreviations

CBT	cognitive behavioral therapy
ES	effect size
OCD	obsessive-compulsive disorder

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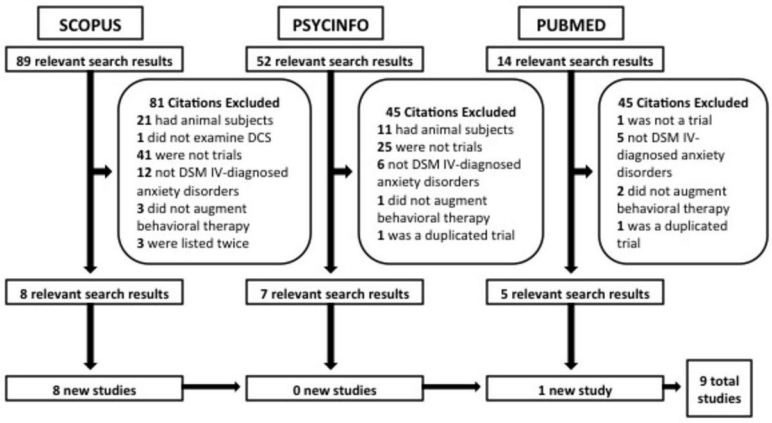

Figure 1.
Selection of Studies

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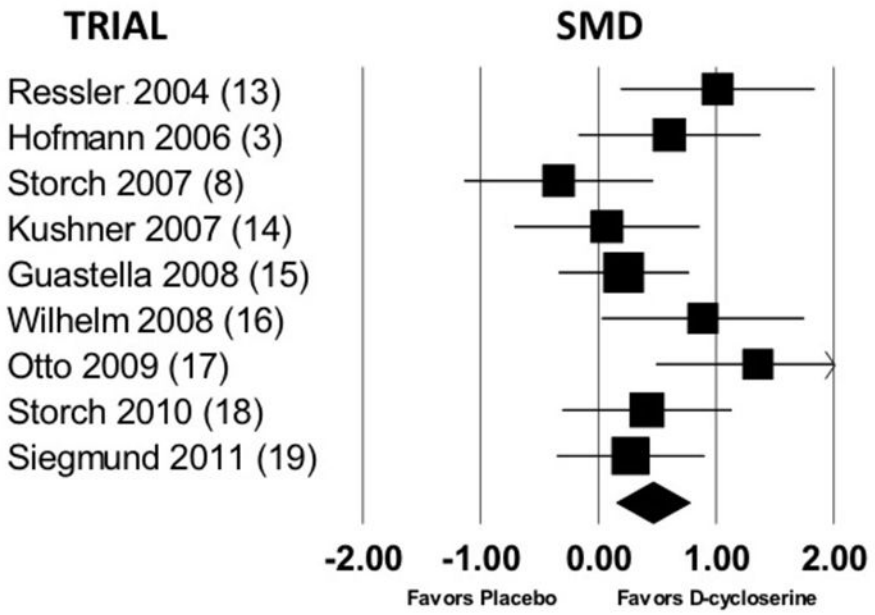

Figure 2. Efficacy of D-cycloserine Augmentation of Behavioral Therapy in the Treatment of Anxiety Disorders

D-cycloserine augmentation demonstrated a significant benefit for treating anxiety disorders (SMD=0.46 (95% CI: 0.15–0.77), z=2.89, p=0.004). There was modest, although not statistically significant, evidence of heterogeneity between trials (I^2=36%, Q=12.6, df=8, p=0.12).

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Table 1

Characteristics of Included Trials

Study	Diagnosis	Dose, mg	hours prior	DCS doses	Therapy	# of exposure sessions	Total therapy sessions	N	Child/ Adult	Analysis	Primary outcome
Ressler 2004 (13)	Acrophobia	275	3	2	VRE	2	2	27	Adult	ITT	SUDS
Hofmann 2006 (3)	SAD	50	1	4	ET	4	5	27	Adult	Completer	SPAI
Storch 2007 (8)	OCD	250	4	12	ERP	10	12	24	Adult	Completer	Y-BOCS
Kushner 2007 (14)	OCD	125	2	4	ERP	4	4	25	Adult	ITT	Y-BOCS
Guastella 2008 (15)	SAD	50	1	4	ET	4	5	50	Adult	ITT	SPAI
Wilhelm 2008 (16)	OCD	100	1	10	ET	10	10	23	Adult	ITT	Y-BOCS
Otto 2009 (17)	PD	50	1	3	CBT	4	5	28	Adult	Completer	PDSS
Storch 2010 (18)	OCD	50	1	7	CBT	7	10	30	Child	ITT	CY-BOCS
Siegmund 2011 (19)	PD	50	1	3	CBT	3	11	39	Adult	Completer	PAS

SAD, Social Anxiety Disorder; PD, panic disorder; VRE, virtual reality exposure; ET, exposure therapy; ERP, exposure and response prevention; SUDS, subjective units of discomfort; SPAI, Social Phobia and Anxiety Inventory; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; PDSS, Panic Disorder Severity Scale; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale, PAS, panic and agoraphobia scale

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