D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders: a meta-analysis
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CRD summary
The authors concluded that D-cycloserine seemed to be an effective addition to behaviour therapy for anxiety disorders. Given the unknown risk of bias and the lack of evidence, the authors’ conclusions seem overly strong.

Authors’ objectives
To evaluate the efficacy of the addition of D-cycloserine to behavioural therapy, for anxiety disorders.

Searching
PubMed, PsycINFO, and Scopus were searched to June 2011, with no language restrictions. Search terms were reported. Reference lists of related reviews, meta-analyses and included articles, were handsearched for further studies.

Study selection
Eligible studies were placebo randomised controlled trials (RCTs), reporting the efficacy of the addition of D-cycloserine to behavioural therapy for anxiety disorders. To be included, trials had to report double blinding in their methods. The primary outcome of interest was the mean improvement in the scores on the primary rating scales of anxiety that were used.

All but one of the included trials were of adults; the other trial was of children. Most patients were diagnosed with obsessive compulsive disorder; some were diagnosed with acrophobia (fear of heights), social anxiety disorder, or panic disorder. The behavioural therapies were virtual reality exposure, exposure with or without response prevention, and cognitive-behavioural therapy. The time from D-cycloserine administration to behavioural therapy ranged from one to four hours. The dose and frequency of D-cycloserine varied across trials, as did the measures of anxiety (reported in paper) and the number of behavioural therapy sessions.

The authors did not state the number of reviewers involved in the selection of studies.

Assessment of study quality
The authors assessed the quality of the included trials, using the Jadad Scale.

Data extraction
The mean improvements in scores on the primary anxiety rating scales were extracted to calculate standardised mean differences and 95% confidence intervals. Any missing information was obtained from the trial investigators.

The authors did not state the number of reviewers involved in data extraction.

Methods of synthesis
Standardised mean differences and 95% confidence intervals from individual studies were pooled using random-effects meta-analysis. Between-study heterogeneity was assessed using Cochran Q and $I^2$.

Defined subgroup analyses were performed for the diagnosed anxiety disorder, and the analysis method (completers versus intention-to-treat). Meta-regression was performed to explore the association between D-cycloserine efficacy and various trial characteristics, such as dosing and timing of D-cycloserine, length of behavioural therapy, methodological quality, and sample size. This sample size analysis was used to assess publication bias, as were funnel plots and the Egger test.

Results of the review
Nine RCTs were included in the review, with 273 participants (range 23 to 50). No quality assessment results were reported.
Compared with placebo, D-cycloserine enhanced the effect of behavioural therapy (SMD 0.46, 95% CI 0.15 to 0.77; nine RCTs); this was statistically significant. Moderate statistical heterogeneity was found between the trials ($I^2=36\%$). A fixed-effect meta-analysis, of the same data, demonstrated a similar pooled result. No evidence of publication bias was found.

When restricted to patients with obsessive compulsive disorder (four RCTs) or social phobia (two RCTs) there was no significant benefit of D-cycloserine; the benefit remained significant for all other subgroups. The meta-regression showed that there were no significant associations between D-cycloserine and any of the variables investigated (full results were presented).

**Authors’ conclusions**
D-cycloserine seemed to be an effective addition to behavioural therapy for anxiety disorders.

**CRD commentary**
The review question was clear and it was supported by well-defined inclusion criteria. Relevant databases were searched, with no language restrictions. No search for grey or unpublished literature was reported, so it is possible that relevant trials were missed. It was unclear how many reviewers were involved in the review processes, and whether these processes were performed independently, thus reviewer error and bias was possible. Quality assessment was reportedly performed, but no results were presented, leaving the possible bias within trials unclear.

Trial details were presented and the methods of synthesis seem to have been appropriate. Extensive effort was made to explore the heterogeneity between trials, but it remained unexplained. Many variables were assessed in a meta-regression with just a few trials (nine), which limits the reliability of the results per variable. Only two trials investigated the same combination of diagnosis, D-cycloserine treatment regimen, and outcome, limiting the generalisability of the overall pooled result, and the reliability of the subgroup analyses. The authors acknowledged that only a limited number of trials could be included in the review.

Given the unknown risk of bias and the lack of evidence, the authors’ conclusions seem overly strong.

**Implications of the review for practice and research**

**Practice:** The authors stated that the lack of a significant association between the number of sessions and the efficacy of the addition of D-cycloserine could have important clinical implications. D-cycloserine could have a consistent significant effect for patients given long-term cognitive-behavioural therapy, for anxiety disorders.

**Research:** The authors stated that further research was needed to investigate the moderators of the D-cycloserine treatment effects. Particularly the influence of anxiety disorder types, the types of therapy, and the interaction between time of treatment and the treatment effect. Such trials could provide a more precise estimate of the treatment effect.

**Funding**
Funding received from the US National Institutes of Health, the American Academy of Child and Adolescent Psychiatry, Eli Lilly, the Trichotillomania Learning Center, and NARSAD.

**Bibliographic details**

**PubMedID**
22579153

**DOI**
10.4088/JCP.11r07356

**Original Paper URL**
http://article.psychiatrist.com/dao_1-login.asp?ID=10007834&am;RSID=12146862213147
Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Anxiety Agents /administration & dosage /therapeutic use; Anxiety Disorders /drug therapy /therapy; Behavior Therapy /methods; Combined Modality Therapy; Cycloserine /administration & dosage /therapeutic use; Humans; Treatment Outcome

AccessionNumber
12012026032

Date bibliographic record published
27/07/2012

Date abstract record published
10/05/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.