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D-Cycloserine Augmentation of Exposure-Based Cognitive Behavior Therapy for Anxiety, Obsessive-Compulsive, and Posttraumatic Stress Disorders

A Systematic Review and Meta-analysis of Individual Participant Data

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IMPORTANCE Whether and under which conditions D-cycloserine (DCS) augments the effects of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders is unclear.

OBJECTIVE To clarify whether DCS is superior to placebo in augmenting the effects of cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders and to evaluate whether antidepressants interact with DCS and the effect of potential moderating variables.

DATA SOURCES PubMed, EMBASE, and PsycINFO were searched from inception to February 10, 2016. Reference lists of previous reviews and meta-analyses and reports of randomized clinical trials were also checked.

STUDY SELECTION Studies were eligible for inclusion if they were (1) double-blind randomized clinical trials of DCS as an augmentation strategy for exposure-based cognitive behavior therapy and (2) conducted in humans diagnosed as having specific phobia, social anxiety disorder, panic disorder with or without agoraphobia, obsessive-compulsive disorder, or posttraumatic stress disorder.

DATA EXTRACTION AND SYNTHESIS Raw data were obtained from the authors and quality controlled. Data were ranked to ensure a consistent metric across studies (score range, 0-100). We used a 3-level multilevel model nesting repeated measures of outcomes within participants, who were nested within studies.

RESULTS Individual participant data were obtained for 21 of 22 eligible trials, representing 1047 of 1073 eligible participants. When controlling for antidepressant use, participants receiving DCS showed greater improvement from pretreatment to posttreatment (mean difference, −3.62; 95% CI, −0.81 to −6.43; $P = .01$; $d = -0.25$) but not from pretreatment to midtreatment (mean difference, −1.66; 95% CI, −4.92 to 1.60; $P = .32$; $d = -0.14$) or from pretreatment to follow-up (mean difference, −2.98, 95% CI, −5.99 to 0.03; $P = .05$; $d = -0.19$). Additional analyses showed that participants assigned to DCS were associated with lower symptom severity than those assigned to placebo at posttreatment and at follow-up. Antidepressants did not moderate the effects of DCS. None of the prespecified patient-level or study-level moderators was associated with outcomes.

CONCLUSIONS AND RELEVANCE D-cycloserine is associated with a small augmentation effect on exposure-based therapy. This effect is not moderated by the concurrent use of antidepressants. Further research is needed to identify patient and/or therapy characteristics associated with DCS response.

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Supplemental content

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Anxiety, obsessive-compulsive, and posttraumatic stress disorders constitute the most prevalent group of mental disorders, collectively affecting up to 30% of individuals at some point in their lives.[1] These conditions contribute significantly to the global burden of disease and disability-adjusted life-years.[2]

First-line treatments for these conditions include cognitive behavior therapy (CBT), typically involving exposure to feared stimuli,[3-9] and medication, primarily selective serotonin reuptake inhibitors.[3-10] While there is ample support for the efficacy of CBT and selective serotonin reuptake inhibitors, a substantial proportion of patients do not achieve sufficient symptom relief and require additional long-term care. In general, the combination of these treatment modalities is not superior to CBT alone in the long run[11-13] and may in fact have deleterious effects and result in increased relapse rates after discontinuation of medication.[14,15] In light of these results, researchers have begun exploring other ways to augment the effects of CBT.[16,17]

One promising strategy is the administration of D-cycloserine (DCS), a partial *N*-methyl-D-aspartate agonist that facilitates fear extinction in animals and reduces return of fear when given before or shortly after extinction training.[16] Despite several initial trials showing promising results in humans with anxiety disorders,[18-20] larger trials conducted within the past 5 years[21,22] have produced mixed results.[23-26] Research suggests that DCS may only enhance CBT under certain conditions.[21,22,27] Variables, such as the number of CBT sessions, the dose and number of DCS administrations, the timing of drug administration, the success of the exposure sessions, or compliance with between-session homework assignments, may also contribute to the conflicting results obtained to date.[26] Further, a large trial in obsessive-compulsive disorder[22] found a significant interaction effect between DCS and antidepressant medication in a post hoc analysis; concomitant antidepressants impaired treatment response in patients randomized to DCS but not in patients randomized to placebo. These results, which are consistent with the animal literature,[28-30] suggest that DCS may only be indicated in patients who are not receiving antidepressants, but these results require replication.

The primary aims of this 1-stage individual participant data (IPD) meta-analysis were to help clarify whether DCS is superior to placebo in augmenting the effects of CBT for anxiety disorders after adjusting for antidepressant use and to evaluate whether antidepressants interact with DCS to reduce its facilitating effects on CBT. Secondary aims were to examine how the following variables affect or moderate the effects of DCS: age, sex, age group (child vs adult), primary diagnosis, number of exposure sessions, DCS dose, timing of administration, and number of DCS administrations. Additionally, we examined whether DCS led to faster improvement of symptoms by examining the effect of DCS vs placebo at midtreatment. Individual-participant data meta-analyses are considered the gold standard of meta-analysis and offer a number of important advantages over traditional meta-analyses that rely on summary statistics, including the better control of patient-level and study-level confounders and increased power for detecting interaction effects and subgroup analyses.[31,32]

Key Points

Question Does D-cycloserine (DCS) augment the effects of exposure-based therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders?

Findings In this meta-analysis of individual participant data from 21 trials, when controlling for antidepressant use, participants receiving DCS showed greater improvement from pretreatment to posttreatment but not from pretreatment to midtreatment or from pretreatment to follow-up. Effect sizes were small, and antidepressants did not moderate the effects of DCS.

Meaning Further research is needed to identify patient and/or therapy characteristics associated with the DCS augmentation effect.

Methods

Protocol and Registration

The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (checklist and protocol).[31] The study protocol was registered with PROSPERO (CRD42015025359) and it is accessible from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015025359.

Eligibility Criteria

Studies were eligible for inclusion if they were (1) published or unpublished double-blind, randomized, placebo-controlled trials of DCS as an augmentation strategy for CBT or behavior therapy incorporating exposure or exposure with response prevention techniques or experimental studies including a single-exposure session and (2) conducted with humans with a diagnosis of specific phobia, social anxiety disorder, panic disorder with or without agoraphobia, obsessive-compulsive disorder, or posttraumatic stress disorder. For the specific phobia studies, the impairment/interference criterion required for the diagnosis was waived to allow the inclusion of fearful individuals who were not significantly impaired given the sporadic appearance of the phobic stimulus in their daily lives.

Information Sources and Search

Two authors (B.M. and A.P.-V.) conducted an independent systematic, 2-step literature search to identify relevant articles. First, PubMed, EMBASE, and PsycINFO were searched from inception to February 10, 2016. Second, manual searches of the reference lists of eligible articles and previous reviews and meta-analyses of aggregate data were performed. Additionally, key authors in the field were contacted for unpublished data.

The search was performed using search algorithms including the terms *D-cycloserine* [and related terms]; *CBT*, *behavior therapy*, or *exposure therapy* [and related terms]; and any of the diagnoses of interest (eMethods 1 in the Supplement). No restrictions were set. Results from the 3 blocks were combined and duplicates removed.

Study Selection and Data Collection Processes

Eligibility of trials was assessed independently by 2 authors (B.M. and A.P.-V.). Any differences in opinion regarding eligibility were resolved by discussion.

Corresponding authors of all eligible studies were contacted and informed via email. Those who were able to contribute were asked to provide anonymized data from their studies using a prespecified template. Data from the individual studies provided were quality controlled and subsequently merged for analysis. For those studies where IPD was not available, data items were extracted from the publications.

Data Items

The requested IPD included the anonymous participant number, sex, age, condition (DCS vs placebo), number of DCS or placebo administrations, time of pill administration (ie, number of minutes before/after the exposure sessions), DCS dose (in milligrams), concomitant antidepressant medication (present/absent, drug name, and dose), number of CBT sessions, and outcomes at major treatment time points (baseline, midtreatment, posttreatment, and follow-up) as measured by the primary outcome measure stipulated by the authors in each individual study. Because different primary outcome measures had different score ranges and data distributions across studies, outcome measures were harmonized. Specifically, we transformed the original data into ranked data to ensure a common metric across studies (score range, 0-100). This is described in detail in the eMethods 2 in the Supplement.

Individual Participant Data Integrity

Two authors (B.M. and L.F.C.) independently assessed IPD data sets, with queries resolved by a third author (D.M.-C.). The data were checked with respect to range, missing or extreme values, errors, and consistency with the published data. Trial details, such as randomization methods and intervention details, were crosschecked against the original publications. Inconsistencies or missing data were discussed and resolved with the collaborators. Each trial was checked individually, and the trial data were sent to the original authors for verification.

Risk of Bias Assessment in Individual Studies and Across Studies

Eligibility criteria were prospectively defined, and all relevant published and unpublished trials were sought to avoid bias. We checked for unusual allocation patterns or distributions of participant characteristics and checked whether there were trials with inappropriate allocation. We established whether any randomized participant data were not included in the data sets (eg, if authors conducted analyses based on completers only, we requested all data on randomized patients in order to perform intent-to-treat analyses). We excluded any nonrandomized participants from the data sets. The Cochrane Collaboration Tool for Assessing Risk of Bias[33,34] was used (post hoc) to explore possible bias in the individual studies.

Synthesis Methods

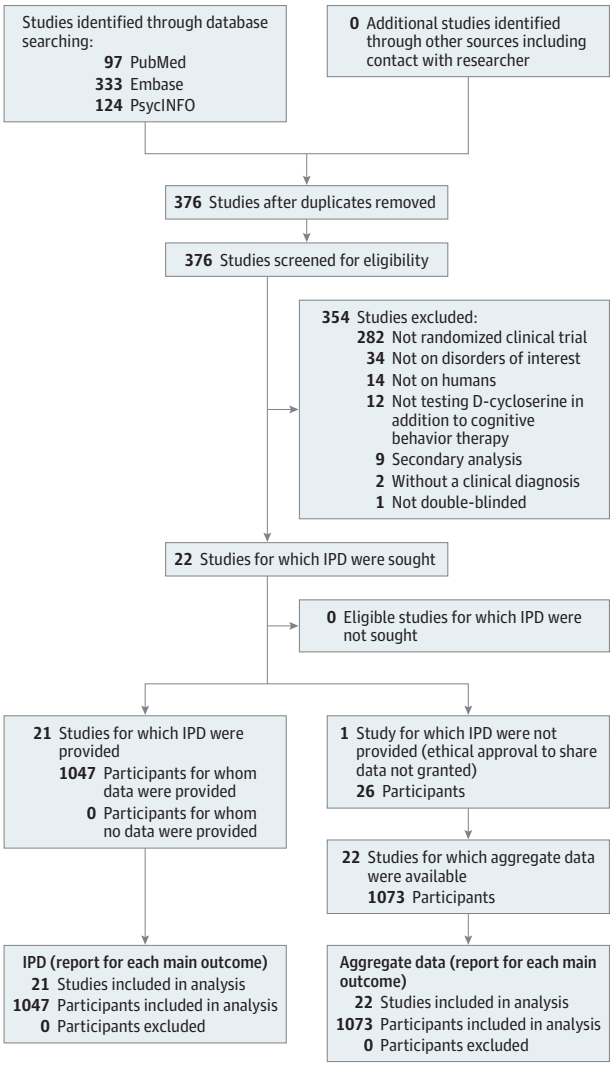
We conducted a 1-stage IPD meta-analysis. We used a 3-level multilevel model (MLM) nesting repeated measures of outcome within participants, who were nested within studies. Our MLM analyses, performed using Hierarchical Linear and Nonlinear Modeling version 7.01 (Scientific Software International Inc), were coded to perform the MLM equivalent of a repeated-measures analysis of covariance, allowing slopes and intercepts to vary between studies and retaining all participants even if they missed assessments or dropped out (ie, intent-to-treat analyses). α Values were 2-tailed, and statistical significance was set at .05.

Our primary analyses examined (1) whether DCS led to greater improvement than placebo after adjusting for antidepressant use and (2) whether antidepressant use moderated the effect of treatment condition (DCS vs placebo) on outcome. Planned secondary analyses examined other possible moderators of the treatment condition effect (listed in the previous section). Post hoc, it was determined that sample size, year of publication, and study quality (risk of bias) were additional variables that were available and may moderate treatment condition effects. Thus, they were added to the moderator analysis.

To model a repeated-measures analysis of covariance in MLM, the growth curve consisted of 3 dummy variables that modeled the change from pretreatment to midtreatment, pretreatment to posttreatment, and pretreatment to follow-up. Each moderator, including antidepressant use, was tested by adding the moderator and the moderator × treatment condition interaction as predictors of the intercept and each of the 3 "slopes" (pretreatment to midtreatment, pretreatment to posttreatment, and pretreatment to follow-up). Moderator variables were converted to *z* scores to facilitate comparison between moderators and to center them at their mean. Treatment group was also centered at its mean. The coding for the dichotomous variables was as follows: group: placebo = 0 and DCS = 1; sex: men = 0 and women = 1; child vs adult studies: child = 0 and adult = 1; and diagnosis: each diagnosis was coded as 1 for that diagnosis and as 0 for other diagnoses. To calculate the timing of administration variable, the start time of the session was subtracted from the time of the administration of the pill, with the result coded in minutes (negative numbers on this scale indicate that DCS was administered before the start of the session, while positive numbers indicate that DCS was administered after the start of the session). Standardized effect sizes (the MLM equivalent of Cohen *d*) were calculated for all significant effects using the techniques developed by Raudenbush and Xiao-Feng[35] or Feingold,[36] as appropriate. Because clinicians and researchers may be specifically interested in the effects of DCS for each type of diagnosis, subgroup analyses were conducted for each primary diagnosis using identical models.

Power analyses, performed using Optimal Design, indicated greater than 0.80 power to detect small effect sizes (Cohen $d = 0.20$) for individual-level effects, including the treatment group effect and individual-level moderators (eg, sex and age). On the other hand, because there were only 21 studies, the power to detect even a large effect size ($d = 0.80$) for the study-level moderators/predictors (eg, sample size and diagnosis) was only approximately 0.70 for single predictors (eg, sample size) and only about 0.40 for diagnosis, which was comprised of 4 dummy variables.

Figure 1. PRISMA Individual Participant Data (IPD) Flowchart for the Study



Results

Study Selection and IPD Obtained

Of the 377 studies that were initially identified and analyzed for eligibility, 22 studies met inclusion criteria (**Figure 1**). The 22 eligible trials included 1073 participants, including 124 with specific phobia, 291 with social anxiety disorder, 77 with panic disorder with or without agoraphobia, 292 with obsessive-compulsive disorder, and 289 with posttraumatic stress disorder.[18-22,37-53] Study characteristics of the 22 eligible studies are presented in eTable 1 in the Supplement.

We were able to obtain IPD from 21 of these 22 studies. Data from 26 participants included in one posttraumatic stress disorder study[50] could not be included because the local ethics committee did not allow data sharing. Therefore, the final data set included 1047 patients (523 receiving DCS and 521 receiving placebo; for 3 additional patients, the group allocation variable was missing), which, to our knowledge, represents 97.6% of the available data. Four of 21 studies were pediatric. The mean (SD) age of the whole sample was 32.1 (13.5) years. The sample was evenly split by sex, with 516 women (49.4%). About one-quarter of the sample (275 [26.9%]) were receiving antidepressants (eTable 2 in the Supplement). The mean (SD) number of treatment sessions was 7.6 (4.5).

IPD Integrity and Risk of Bias Within Studies

Discrepancies between the provided IPD and the original reports were found in 16 of 21 studies. Twenty-nine mismatches were found, most of which were related to different numbers of patients receiving antidepressant medication reported in the publication vs the data set. All discrepancies, except for a mismatch on the medication breakdown in one study (where we assumed that the actual data set was correct) were successfully resolved by correspondence with the authors.

Authors of 5 of the included studies were contacted to request missing data. All missing data were provided except for the age variable in one of the studies.

Corresponding authors of 6 of the eligible studies were contacted to request data on all randomized participants because initially only information on completers had been provided. Data were received for 31 noncompleters who had originally been omitted from the data sets. Additionally, one of the data sets included 2 nonrandomized participants who were excluded prior to analysis.

Results of Individual Studies

Data were obtained for all participants who were initially randomized in each of the studies for which IPD were available. Between-group (DCS vs placebo) Cohen *d* effect sizes and 95% CIs at posttreatment for each individual study based on raw data are shown in eTable 3 in the Supplement.

Results of Syntheses (Primary Aim)

We identified 11 different primary outcomes measures in the included studies (eTable 1 in the Supplement). As expected, the different outcome measures had different ranges and distributions (eFigure in the Supplement), and therefore, the data were transformed to ensure a common measurement across studies (eMethods 2 in the Supplement).

Initial exploratory analyses to determine the overall effect of DCS vs placebo showed that improvement was greater in those who received DCS than those who received placebo from pretreatment to posttreatment (difference, −3.93; 95% CI, −1.16 to −6.70; $P = .006$, $d = -0.27$) and from pretreatment to follow-up (difference, −3.32; 95% CI, −0.34 to −6.30; $P = .03$, $d = -0.21$) but not from pretreatment to midtreatment (difference, −1.69; 95% CI, −1.51 to −4.89; $P = .30$) (eTable 4 in the Supplement). These analyses also showed that participants receiving DCS had lower symptom severity than participants receiving placebo at posttreatment (difference, −3.34; 95% CI, −1.12 to −5.56; $P = .004$, $d = -0.22$) and at follow-up (difference, −2.73, 95% CI, −0.25 to −5.21; $P = .03$; $d = -0.18$) (eTable 4 in the Supplement).

To investigate primary aim 1, we ran this same analysis controlling for antidepressant use as a moderator of the DCS ef-

Table 1. Multilevel Model Coefficients for the Effect of D-Cycloserine vs Placebo in the Augmentation of Exposure-Based Cognitive-Behavior Therapy[a] (Primary Aims 1 and 2)

Predictor	Regression Coefficient (SE)	*P* Value
Intercept	50.33 (0.97)	<.001[b]
Group (DCS/placebo)[c]	0.43 (1.07)	.69
Antidepressants	2.39 (1.31)	.08
Baseline severity	0.60 (0.04)	<.001[b]
Time pretreatment to midtreatment	−24.39 (3.95)	<.001[b]
Time pretreatment to posttreatment	−35.05 (3.85)	<.001[b]
Time pretreatment to follow-up	−36.40 (3.11)	<.001[b]
Group × antidepressants	0.80 (2.43)	.74
Group × time pretreatment to midtreatment	−1.66 (1.67)	.32
Group × time pretreatment to posttreatment	−3.62 (1.44)	.01[b]
Group × time pretreatment to follow-up	−2.98 (1.54)	.05
Antidepressants × time pretreatment to midtreatment	−0.81 (2.19)	.71
Antidepressants × time pretreatment to posttreatment	−2.01 (1.81)	.27
Antidepressants × time pretreatment to follow-up	−4.32 (1.89)	.02[b]
Group × time pretreatment to midtreatment × antidepressants	−2.23 (3.99)	.58
Group × time pretreatment to posttreatment × antidepressants	−3.67 (3.28)	.26
Group × time pretreatment to follow-up × antidepressants	1.19 (3.51)	.73

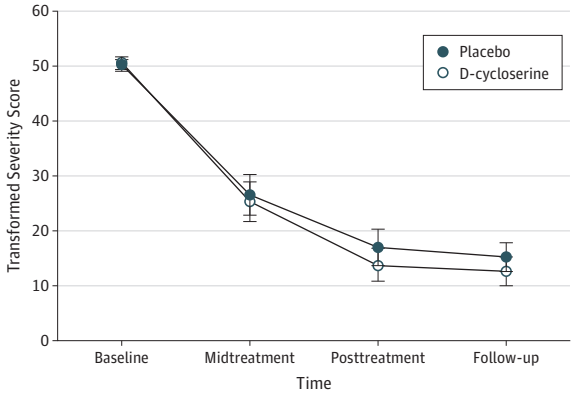
Abbreviation: DCS, D-cycloserine.

[a] Antidepressants were included in the model as an a priori moderator.

[b] These effects were also significant in the final multimoderator analysis.

[c] Group was coded as placebo = 0 and DCS = 1.

Figure 2. Group by Time Interaction Effects on the Transformed Primary Outcome Measure[a]



Scores are shown at baseline, midtreatment, posttreatment, and follow-up, according to treatment group. The vertical axis represents the transformed (ranked) severity score, with higher scores denoting greater symptom severity (range, 0-100). Error bars indicate 95% CIs.

[a] Antidepressants were included in the model as an a priori moderator.

fects (**Table 1**). Participants receiving DCS showed greater improvement than those receiving placebo from pretreatment to posttreatment (difference, −3.62; 95% CI, −0.81 to −6.43, $P = .01$, $d = -0.25$), but not from pretreatment to midtreatment (difference, −1.66, 95% CI, −4.92 to 1.60; $P = .32$; $d = -0.14$) or from pretreatment to follow-up (difference, −2.98; 95% CI, −5.99 to 0.03; $P = .05$; $d = -0.19$) (Table 1; **Figure 2**). Additional post hoc analyses also revealed that participants receiving DCS evidenced lower symptom severity than those receiving placebo at both posttreatment (difference, −3.19; 95% CI, −0.95 to −5.43; $P = .006$; $d = -0.21$) and at follow-up (difference, −2.54; 95% CI, −0.04 to −5.04; $P = .05$; $d = -0.16$).

The same model was used to address primary aim 2. Results showed that antidepressant use did not moderate any of the effects of DCS on outcome (Table 1). However, we did find that regardless of randomized treatment condition, participants taking antidepressants improved more from pretreatment to follow-up than those not taking antidepressants (difference, −4.32; 95% CI, −0.64 to −8.01; $P = .02$, $d = -0.28$) (Table 1).

Moderator Analyses (Secondary Aim)

The random effects for the improvement from pretreatment to midtreatment ($\chi^2_{10} = 144.02$; $P < .001$), pretreatment to posttreatment ($\chi^2_{10} = 150.83$; $P < .001$), and pretreatment to follow-up ($\chi^2_{10} = 1102.70$; $P < .001$) were significant, indicating significant variability in the amount of improvement between studies, hence suggesting the existence of possible moderators. We first examined each moderator separately. We then included all the significant moderators and predictors in a final, composite multimoderator analysis. One moderator was relevant to DCS participants only (DCS dose) and could not be estimated as a moderator in the full sample because it was 0 for all placebo participants. Hence, we could analyze DCS dose only as a predictor and not as a moderator of outcome in a separate analysis.

Results from the individual moderator analyses are presented in **Table 2**. Significant moderators in the individual moderator analyses were then included in the multimoderator analysis. Only 1 significant moderator emerged: year of publication. Specifically, the more recent the study, the smaller the difference between DCS and placebo for pretreatment to follow-up improvement ($b = 4.02$; 95% CI, 0.59-7.45; $P = .02$, $d = 0.26$). Additional post hoc analyses showed that the overall score in the Cochrane Collaboration Tool for Assessing Risk of Bias for each individual study (eResults and eTables 5 and 6 in the Supplement) was not a significant moderator of any of the DCS effects (Table 2).

The analysis of the DCS-relevant predictor, performed using only the DCS subsample, showed that DCS dosage was highly skewed (skewness = 3.89). While 428 of 523 participants (81.8%) received 50 mg of DCS, some received 250 mg or even 500 mg. To reduce skewness to acceptable levels (<1.0),[54] we used the inverse transformation,[54] which reduced skewness to −0.31. The analysis of the transformed DCS dosage showed that it was not associated with the outcome (Table 2).

Risk of Bias Across Studies

To our knowledge, this meta-analysis includes 97.6% of all eligible data. The only missing study[50] failed to find an advantage of DCS

Table 2. Results for Analyses With Each Potential Moderator Tested as an Individual Moderator of Outcome (Secondary Aim)

Predictor	Moderator																					
	Age		Sex		Adult vs Child		Diagnosis[a]		No. of Sessions		Dose Timing		No. of Doses		DCS Dosage[b]		Year Published[c]		Sample Size[c]		Risk of Bias[c]	
	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value	Regression Coefficient	*P* Value
Intercept[d]	50.55	<.001	50.59	<.001	50.51	<.001	50.31	<.001	50.83	<.001	50.08	<.001	50.30	<.001	51.40	<.001	50.42	<.001	49.64	<.001	50.64	<.001
Group (DCS/placebo)	0.56	.61	0.50	.64	0.59	.58	0.59	.58	0.55	.60	0.57	.59	0.44	.68	NA	NA	0.63	.55	0.57	.59	0.59	.58
Moderator	−0.63	.29	1.02	.07	−0.61	.50	2.29	.10	0.54	.48	−1.83	.07	0.97	.15	1.33	.15	−1.12	.23	−2.22	.07	0.71	.36
Baseline severity[d]	0.60	<.001	0.61	<.001	0.60	<.001	0.60	<.001	0.60	<.001	0.60	<.001	0.60	<.001	0.59	<.001	0.61	<.001	0.60	<.001	0.61	<.001
Time pretreatment to midtreatment[d]	−21.65	<.001	−24.81	<.001	−24.65	<.001	−25.13	<.001	−25.52	<.001	−23.42	<.001	−26.12	<.001	−26.86	<.001	−23.15	<.001	−23.21	<.001	−24.93	<.001
Time pretreatment to posttreatment[d]	−36.08	<.001	−35.21	<.001	−34.91	<.001	−34.95	<.001	−35.42	<.001	−32.76	<.001	−34.34	<.001	−37.43	<.001	−34.67	<.001	−33.02	<.001	−35.30	<.001
Time pretreatment to follow-up[d]	−37.52	<.001	−36.77	<.001	−36.51	<.001	−36.50	<.001	−37.08	<.001	−34.65	<.001	−36.09	<.001	−38.81	<.001	−36.31	<.001	−34.66	<.001	−36.87	<.001
Group × moderator	−1.09	.32	−0.32	.76	−1.10	.30	1.46	.38	0.72	.50	0.30	.78	0.57	.60	NA	NA	0.86	.41	0.22	.84	−0.39	.63
Group × time pretreatment to midtreatment	−0.77	.66	−1.60	.33	−2.18	.19	−1.45	.42	−2.34	.22	−1.48	.37	−0.71	.69	NA	NA	−1.75	.29	−1.80	.28	−1.13	.50
Group × time pretreatment to posttreatment[d]	−3.34	.02	−3.78	.008	−3.96	.005	−3.91	.006	−4.27	.003	−3.91	.006	−3.76	.009	NA	NA	−3.89	.006	−3.91	.006	−3.94	.006
Group × time pretreatment to follow-up	−1.65	.30	−3.15	.04	−3.35	.03	−3.27	.03	−4.28	.008	−3.15	.04	−2.99	.06	NA	NA	−3.28	.03	−3.63	.02	−3.23	.04
Moderator × time pretreatment to midtreatment	0.51	.60	−1.21	.15	0.90	.67	−12.90[d]	<.001	−0.81	.67	4.27[d]	.02	−0.19	.91	1.27	.44	5.94	<.001	2.77	.36	−1.15	.53
Moderator × time pretreatment to posttreatment	1.62	.06	−1.75[d]	.02	1.93	.39	−7.57	.03	−4.04	.02	4.05	.07	−3.99	.003	1.30	.41	2.11	.37	4.07	.21	−2.17	.27
Moderator × time pretreatment to follow-up	1.29	.16	−1.90[d]	.02	1.41	.51	−6.49	.04	−2.82	.09	3.40	.09	−2.95	.02	1.82	.30	1.93	.37	4.66	.12	−1.63	.37
Group × time pretreatment to midtreatment × moderator	−0.44	.79	1.87	.26	−1.71	.24	−0.97	.77	0.98	.63	1.60	.29	−2.56	.17	NA	NA	2.32	.17	1.22	.42	−1.08	.35
Group × time pretreatment to posttreatment × moderator	0.83	.57	−0.02	.99	−0.36	.80	−0.22	.92	1.61	.27	0.75	.60	−0.71	.64	NA	NA	2.84	.04	2.17	.12	1.55	.15
Group × time pretreatment to follow-up × moderator	1.75	.27	0.64	.68	0.47	.77	−1.07	.68	2.48	.15	1.81	.23	−1.00	.55	NA	NA	4.59[d]	.002	3.53	.02	−0.34	.77

Abbreviations: DCS, D-cycloserine; NA, not applicable.

[a] There were 5 different diagnoses, which required 4 dummy variables to code the 5 diagnoses (specific phobia was chosen as the "reference" category because it showed the least improvement). The specific coefficients shown for the "moderator" in this column are for obsessive-compulsive disorder, which was the only diagnosis that yielded consistent significant effects compared with specific phobia.

[b] Relevant to DCS only and hence does not have any group effects, any moderator × group interactions, nor any moderator × time × group effects. This variable was inverse-transformed to reduce skewness.

[c] Nonprespecified in the study protocol and added post hoc.

[d] Significant in the final multimoderator analysis.

vs placebo in individuals with posttraumatic stress disorder. In that study, exposure therapy plus placebo performed significantly better than exposure therapy plus DCS, leading to a potential bias in favor of DCS owing to the omission of that study.

Additional Analyses

For more detailed information on the effect of DCS by diagnosis, we ran our primary analysis separately for each diagnosis (eTable 7 in the Supplement). The advantage of DCS over placebo was only significant for those with social anxiety disorder (eTable 7 in the Supplement). Antidepressants significantly moderated DCS effects only for participants with panic disorder with or without agoraphobia, which made up the smallest diagnosis sample in our meta-analysis (n = 77) and included only 2 studies (eTable 1 in the Supplement).

Sensitivity Analyses

We reran our models excluding the single-session studies by Gutner et al[38] and Rodebaugh et al,[41] which were not treatment studies but experimental in nature. In the analysis controlling for antidepressant use as a moderator of the DCS effects (primary aim 1), participants receiving DCS did not show greater improvement from pretreatment to posttreatment (difference, −2.85; 95% CI, −5.91 to 0.21; $P = .06$; $d = -0.21$) (eTable 8 in the Supplement). However, effect sizes were similar to the original analyses ($d = -0.21$ vs $d = -0.25$). Antidepressant use did not moderate any of the effects of DCS on outcome (primary aim 2).

Additionally, we repeated the analyses excluding only the study by Gutner et al,[38] which was the only one including patients who may not have met the impairment/interference criterion for specific phobia. Results after the exclusion of this trial were virtually identical to those reported for the full sample (eTable 8 in the Supplement).

Discussion

The main finding of this 1-stage IPD meta-analysis was that DCS showed a statistically significant advantage over placebo at posttreatment, regardless of the inclusion of treatment with antidepressants in the model. This advantage was small (less than 4 points on a 0-100 scale; $d = -0.25$). Less consistent evidence was found for the advantage of DCS at follow-up. Furthermore, the multimoderator analysis revealed that only publication year was significant, suggesting that more recent studies tended to show smaller differences in improvement between DCS and placebo from pretreatment to follow-up (0.26 SDs less improvement for each additional year).

The acceleration of treatment effects observed in some individual trials at midtreatment[21,55] could not be confirmed because there were no significant midtreatment effects. Our analyses also failed to confirm the hypothesis that concomitant antidepressant medication would moderate the effects of DCS, as initially suggested by the animal literature[28,29] and a 2015 human trial.[22]

The number of treatment sessions did not moderate treatment outcomes. It has been suggested that DCS may offer greater advantage vs placebo when brief treatments are used because the placebo-treated patients have less chances to "catch up" with the DCS-treated patients in brief treatments.[27,56] Our analysis did not support this hypothesis but suggested that the small benefits of DCS at posttreatment are attenuated during follow-up.

The number of DCS pill administrations was not associated with the degree of improvement at any time. This finding is not consistent with the concern that DCS efficacy may decrease with increasing numbers of administrations.[24]

Neither the time of administration nor the dose of DCS had an effect on the outcomes, although there was relatively small variability in the data. Most trials administered the drug approximately 1 hour before the exposure session, and most participants received 50-mg doses.

Although DCS may exert its effects by enhancing fear extinction retention, studies have not limited inclusion to participants with extinction consolidation deficits. Therefore, weak effects across trials are perhaps unsurprising. Similarly, DCS has been administered in these studies independent of within-session learning experiences, a notable weakness given the possibility that DCS may enhance fear memory reconsolidation under certain conditions.[57] Extinction learning varies across sessions and patients, and accordingly, DCS may have inadvertently interfered with exposure efficacy in some patients and facilitated its efficacy in others.[57,58]

Strengths and Limitations

A major strength of this study was that we could obtain more than 97% of all eligible raw data, which greatly surpasses the greater than 90% of eligible participants that has been suggested as a suitable target to achieve.[59] A power calculation revealed that, with our combined sample size, we had greater than 80% power to detect an effect size as small as a Cohen *d* value of 0.20 for the treatment effects and individual-level moderators. This represents a substantial improvement on previous aggregate-data meta-analyses,[23-26,60] which were only powered to detect large effect sizes.

This study also had limitations. We had less power to detect study-level moderators/predictors and for subgroup analyses. Similarly, there have only been 4 studies using pediatric samples, which limits the generalizability of our results to younger populations. Another limitation is that different studies used different outcome measures, and for this reason, these had to be transformed into ranked scores to ensure a single metric across studies. Finally, we could not examine in-session experiences as possible moderators of DCS efficacy. For example, fear at the end of an exposure therapy session has emerged as 1 possible important variable[57] because it has been shown to moderate DCS efficacy in 2 studies[58,61] as well as the efficacy of 2 other pharmacological enhancement strategies (yohimbine[62] and methylene blue[63]).

Conclusions

We found evidence supporting the short-term superiority of DCS vs placebo in the augmentation of exposure-based CBT

for anxiety-related disorders and mixed support for the maintenance of these benefits at follow-up. While statistically significant, the effect sizes were small. Concomitant antidepressant medication did not significantly moderate the effects of DCS. None of the prespecified patient-level (eg, age and sex) or study-level (eg, primary diagnosis, number of exposure sessions, DCS dose, timing of administration, and number of DCS administrations) moderators were clearly associated with outcomes. The limitations of previous studies and lessons learned over the past decade call for a next stage of research examining the efficacy of DCS and other augmentation strategies for facilitating exposure therapy, which specifically examines targeted administration as guided by theory and basic research findings.[27,64,65]

ARTICLE INFORMATION

Correction: This article was corrected on March 15, 2017 to fix errors in the subtitle, group author information, Key Points, Methods section, and Results sections of the Abstract and text.

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