A Meta-Analysis of D-Cycloserine in Exposure-Based Treatment: Moderators of Treatment Efficacy, Response, and Diagnostic Remission

Joseph F. McGuire, PhD[a,*]; Monica S. Wu, MA[b,c]; John Piacentini, PhD[a]; James T. McCracken, MD[a]; and Eric A. Storch, PhD[b,c,d,e,f,g]

ABSTRACT

Objective: This meta-analysis examined treatment efficacy, treatment response, and diagnostic remission effect sizes and moderators of D-cycloserine–augmented exposure treatment in randomized controlled trials (RCTs) of individuals with anxiety disorders, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD).

Data Sources and Study Selection: The terms D-*cycloserine* AND *randomized controlled trial* were used to search the PubMed (1965–May 2015), PsycINFO, and Scopus databases for randomized placebo-controlled trials of D-cycloserine–augmented exposure therapy for anxiety disorders, OCD, and PTSD.

Data Extraction: Clinical variables and effect sizes were extracted from 20 RCTs (957 participants). A random-effects model calculated the effect sizes for treatment efficacy, treatment response, and diagnostic remission using standardized rating scales. Subgroup analyses and meta-regression were used to examine potential moderators.

Results: A small, nonsignificant benefit of D-cycloserine augmentation compared to placebo augmentation was identified across treatment efficacy ($g = 0.15$), response (risk ratio [RR] = 1.08), and remission (RR = 1.109), with a moderately significant effect ($P = .03$) for anxiety disorders specifically ($g = 0.33$). At initial follow-up assessments, a small, nonsignificant effect size of D-cycloserine augmentation compared to placebo was found for treatment efficacy ($g = 0.21$), response (RR = 1.06), and remission (RR = 1.12). Specific treatment moderators (eg, comorbidity, medication status, gender, publication year) were found across conditions for both acute treatment and initial follow-up assessments.

Conclusions: D-Cycloserine does not universally enhance treatment outcomes but demonstrates promise for anxiety disorders. Distinct treatment moderators may account for discrepant findings across RCTs and disorders. Future trials may be strengthened by accounting for identified moderators in their design, with ongoing research needed on the mechanisms of D-cycloserine to tailor treatment protocols and maximize its benefit.

J Clin Psychiatry 2017;78(2):196–206
dx.doi.org/10.4088/JCP.15r10334

[a]Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles
[b]Departments of Psychology, [c]Pediatrics, [d]Psychiatry and Behavioral Neurosciences, and [e]Health Policy and Management, University of South Florida, Tampa
[f]Rogers Behavioral Health—Tampa Bay, Tampa, Florida
[g]All Children's Hospital, Johns Hopkins Medicine, St Petersburg, Florida
**Corresponding author:* Joseph F. McGuire, PhD, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, 760 Westwood Plaza, 48-228B, Los Angeles, CA, 90095 (jfmcguire@mednet.ucla.edu).

Anxiety disorders, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) are characterized by clinically significant fear and distress that occur in response to stimuli or situational cues.[1] These psychiatric conditions collectively affect between 2% and 29% of individuals.[2,3] Psychiatric comorbidity is common for these conditions, with co-occurring anxiety and depressive disorders frequently endorsed by individuals.[4] Although these disorders possess distinctive diagnostic features and multifactorial etiologies,[1] the mechanisms of fear conditioning and extinction are believed to play a central role in symptom acquisition, persistence, and treatment.[5]

Cognitive-behavioral therapy (CBT) is an efficacious treatment for anxiety disorders, OCD, and PTSD, with the core therapeutic component being exposures to feared situations or stimuli.[6] Although efficacious, exposure-based CBT for these disorders has several limitations. These challenges include inadequate response to exposure-based therapies and infrequent diagnostic remission, treatment attrition and treatment burden, and limited access and availability to trained treatment providers experienced in conducting exposure-based CBT with anxious patients.[7,8] Taken together, there is a clear need to improve therapeutic outcomes and accelerate treatment gains to reduce patient burden and improve therapist availability.

Multiple approaches have been explored to enhance or accelerate treatment outcomes for youth and adults with anxiety disorders, OCD, and PTSD. One approach involves the administration of cognitive enhancers to augment exposure-based therapies. Broadly, cognitive enhancers are compounds that influence signaling pathways in brain regions associated with fear learning to enhance neurocircuitry of fear extinction that occurs during exposure-based treatments.[9] Although multiple cognitive enhancers have been evaluated in randomized controlled trials (RCTs) among individuals with fear-based psychiatric disorders,[8] D-cycloserine is the most well-studied cognitive enhancer in both youths and adults. D-Cycloserine is a partial *N*-methyl-D-aspartate (NMDA) agonist that has been found to enhance fear extinction in animal studies.[10,11] It is believed that acute D-cycloserine administration stimulates NMDA glutamate synapses involved in emotional learning and strengthens extinction learning that takes place in exposure-based treatments,[12,13] which may occur in part through the consolidation of extinction learning.[14] Given the parallels between fear extinction in animal studies and

human exposure-based therapies, D-cycloserine has been evaluated across multiple RCTs with mixed success.[15–34]

When evaluating the benefit of a treatment approach, synthesizing the empirical evidence is important to inform clinical decisions.[35] Meta-analyses provide a quantitative synthesis of RCTs and can examine treatment moderators across studies. To date, 4 meta-analyses[10,36–38] have examined the efficacy of D-cycloserine–augmented exposure-based therapies relative to placebo augmentation across anxiety disorders, OCD, and PTSD. Norberg and colleagues[10] examined D-cycloserine across animal and human studies. Although a large effect was found in animal studies ($d = 1.19$), the augmentative effects of D-cycloserine were modest among clinical human studies at posttreatment ($d = 0.60$) and follow-up assessments ($d = 0.47$).[10] Meanwhile, Bontempo and colleagues[36] completed a meta-analysis of 9 RCTs with 273 human participants and found a standardized mean difference (SMD) of 0.46 between D-cycloserine–augmented and placebo-augmented treatment at posttreatment. Rodrigues and colleagues[37] completed a meta-analysis of 13 RCTs and found a small effect (SMD = 0.34) of D-cycloserine–augmented treatment relative to placebo augmentation at posttreatment. Most recently, Ori and colleagues[38] completed a meta-analysis of 21 RCTs and found no significant difference in treatment response between D-cycloserine augmentation and placebo augmentation treatment (risk ratio [RR] = 1.1; 95% CI, 0.89 to 1.34). While these meta-analyses initially suggest an overall benefit of D-cycloserine in augmenting exposure-based treatments, the additive benefit of D-cycloserine appears to have diminished with the inclusion of further RCTs. This diminishing effect may be attributed to a minimal benefit of D-cycloserine revealed with further examination, trial design methodologies of later RCTs that utilized full courses of exposure treatments, or possible moderators that influence treatment effects.

Notably, across these 4 meta-analyses, few moderators have been examined. Available moderator analyses have found no association between treatment effects and dose,[10,36] time of administration,[36] number of doses,[10,36] number of treatment sessions,[36] diagnostic group,[36] methodological quality,[36] and analytic method.[36] However, Norberg and colleagues[10] found that D-cycloserine doses administered closer to therapy sessions exhibited greater effects. Although these prior examinations are noteworthy, they include several limitations: small sample size,[36] moderator analyses across humans and animal studies,[10] and treatment effect extraction from ratings with untested psychometric properties (eg, subjective fear ratings).[10,36] Additionally, the moderating influence of gender, co-occurring psychiatric conditions, or concurrent medication status was not examined. Furthermore, there has been no evaluation of moderators of treatment response and diagnostic remission.

To address these concerns, this report examined placebo-controlled RCTs of D-cycloserine–augmented exposure-based treatment for anxiety disorders, OCD, and PTSD to determine its treatment efficacy and to identify the RR of experiencing treatment response or diagnostic remission. We hypothesized that D-cycloserine–augmented exposure-based treatment would outperform placebo-augmented exposure-based treatment. Based on prior meta-analyses and the extant literature, several theoretically derived moderators were examined. First, given the neurobiological differences in fear acquisition and extinction between youth and adults,[39] we examined the influence of age. Second, given the variable gender distribution across studies (19%–100%), we examined whether gender influenced treatment effects. Third, as specific disorders (ie, panic disorder, PTSD, depression) have been related to impediments in fear acquisition and extinction,[40] we examined whether co-occurring anxiety or depressive disorders influenced effects. Fourth, as serotonin reuptake inhibitors (SRIs) are common evidence-based treatments for these conditions and have demonstrated mixed evidence on the promotion and impairment of fear extinction,[41,42] we examined the moderating impact of SRIs on treatment effects. Fifth, as some studies utilized full courses of treatment and others employed abbreviated treatment protocols, we examined the influence of therapeutic contact on treatment effects. Finally, following up on studies that suggest that dose[15,43] and time administration[10] may influence D-cycloserine outcomes, we investigated whether these factors impacted treatment effects.

Clinical Points

- Given the mixed findings among randomized controlled trials of D-cycloserine augmentation of exposure-based treatments, possible moderators of D-cycloserine augmentation were examined.
- In contrast to previous meta-analyses, a minimal benefit was observed for D-cycloserine for augmenting exposure-based treatments for anxiety disorders, with no significant benefit for obsessive-compulsive disorder and posttraumatic stress disorder.
- Moderator analyses identified several significant moderators within and across disorders that explain discrepant findings and warrant further examination.

METHODS

Search Strategy

PubMed (1965–May 2015), PsycINFO, and Scopus were searched using the key search terms *D-cycloserine* and *randomized controlled trial*. Identified abstracts were reviewed independently by 2 raters (J.F.M. and M.S.W.) for appropriateness. The references of eligible treatment trials and review articles were also searched. Identified abstracts and citations were evaluated with the following inclusion criteria: (1) an RCT; (2) comparison of D-cycloserine–augmented exposure-based treatment to placebo-augmented exposure-based treatment; (3) sample that met criteria for an anxiety disorder, OCD, or PTSD; (4) article available in English; and (5) provision of sufficient data to calculate treatment effects using psychometrically supported rating

scales. When insufficient or incomplete data were present, study investigators were contacted to obtain values.

Procedures

Given the diversity of measures across studies, a hierarchy of preferred informant ratings for the primary outcome measure was established a priori to limit reporting bias. In order of preference, these informants included clinician ratings, self-report ratings, and parent-reported ratings. When multiple ratings by the same informant were available, preference was placed on the most commonly used measure in RCTs. For classification of treatment response, preference was placed on the Clinical Global Impressions-Improvement scale (CGI-I),[44] with treatment response classified as a rating of "much improved" or "very much improved." When the CGI-I was unavailable, a percent reduction or clinical cutoff score based on the primary outcome measure was selected that corresponded with a response on the CGI-I.[45–49] For classification of diagnostic remission, preference was placed on the Clinical Global Impressions-Severity of Illness scale (CGI-S), with a remission rating classified as a rating of "no illness" or "mild illness."[44,50] When the CGI-S was unavailable, a percent reduction or clinical cutoff score based on the primary outcome measure was selected that corresponded with a categorization of remission on the CGI-S.[45–47]

Trials were coded for the following characteristics: sample size, percentage male, average participant age, percentage of co-occurring anxiety or depressive disorders, percentage on an SRI medication, number of therapy sessions, D-cycloserine administration time and number of D-cycloserine doses, publication year, and analysis type (intent-to-treat or completer). Study methodology was assessed using a 23-item scale that has been used in other meta-analyses,[51,52] with higher scores corresponding to greater methodological rigor. Trials were coded by 2 raters to ascertain reliability. Rater disagreement was resolved through discussion and consensus.

Effect Size Calculation

Given the difference in sample sizes across studies, Hedges *g* was used to calculate treatment efficacy and was calculated in Comprehensive Meta-Analysis (CMA) 2nd Edition.[53] Effect sizes were calculated using change scores because they increase the precision of effect size estimators by controlling for pretreatment group differences of symptom severity. Pretreatment and posttreatment means and standard deviations were entered into CMA and were divided by the pooled posttreatment standard deviation. Effect sizes were standardized so that a positive result indicated that D-cycloserine outperformed placebo augmentation in reducing symptom severity. The RR is the ratio of participants exhibiting response or remission with D-cycloserine–augmented treatment divided by the probability of patients exhibiting response or remission with placebo-augmented treatment.[54] A RR of 1 suggests that response or remission did not differ between conditions, whereas a RR of 3 indicates that the D-cycloserine augmentation had a 3-fold greater probability of exhibiting response or remission. The number of participants experiencing a treatment response and remission were entered into CMA, which calculated the RR for treatment response and diagnostic remission.

Statistical Analyses

Interrater agreement of study characteristics and quality ratings were assessed using descriptive statistics and intraclass correlation coefficient (ICC). A random-effects model using inverse variance weights examined the effect size of D-cycloserine–augmented treatment. Separate random-effects models examined the RR of D-cycloserine–augmented treatment for treatment response and diagnostic remission. A random-effects model was chosen because the true effect size was expected to vary across trials due to different study characteristics.[55] Heterogeneity of effect size was assessed using the forest plot, *Q* statistic, and I^2 statistic. Publication bias was assessed by visual inspection of the funnel plot and Egger test for bias. When publication bias was present, a trim-and-fill method was applied to account for bias by producing an adjusted summary effect that takes into account possibly unpublished studies within the field.[55] Finally, moderator variables were analyzed using either method-of-moments meta-regression or an analog to the analysis of variance (ANOVA).

RESULTS

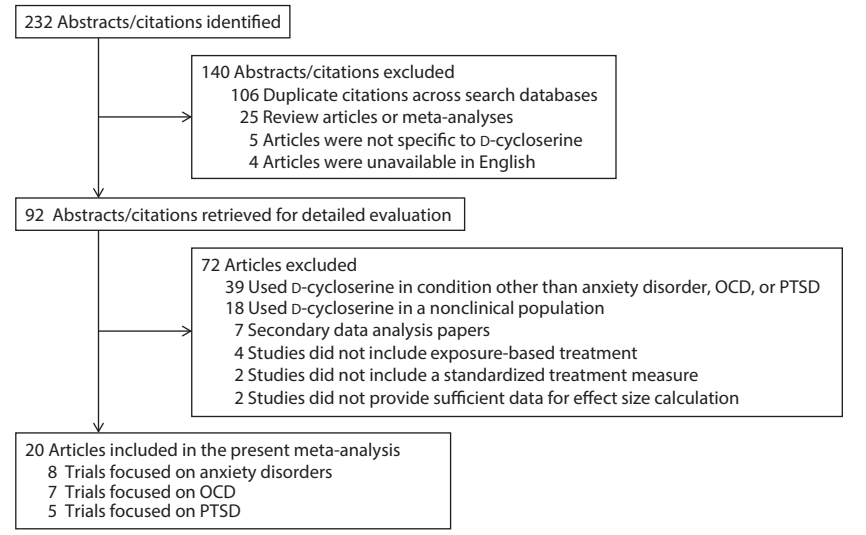
Included Studies and Reliability Ratings

Initial search strategies produced 232 potential abstracts/citations, with 92 abstracts being retrieved for detailed review (Figure 1). Table 1 displays the 20 RCTs (anxiety, 8 studies; OCD, 7 studies; PTSD, 5 studies) that met inclusion criteria and produced a final sample size of 957 participants. The average initial follow-up assessment occurred 2.30 months after acute treatment (range, 1–6). There was excellent interrater agreement between the 2 raters on categorical and continuous study characteristics (100% agreement), as well as overall study methodological quality (ICC = 0.94; 95% CI, 0.86 to 0.98).

D-Cycloserine–Augmented Outcomes

Acute efficacy. A random-effects meta-analysis found a nonsignificant effect for D-cycloserine–augmented relative to placebo-augmented treatment across all studies ($g = 0.15$; 95% CI, −0.03 to 0.32; $z = 1.65$; $P = .10$) (Figure 2). Visual inspection of the forest plot, *Q* statistic, and I^2 statistic identified significant heterogeneity ($Q_{18} = 29.09$, $P = .05$, $I^2 = 38.12\%$). Visual inspection of the funnel plot and Egger test for bias indicated that publication bias was not significant ($t = 0.95$, $P = .36$). When diagnostic groups were examined separately, there was a moderately significant effect for anxiety disorders ($g = 0.33$; 95% CI, 0.02 to 0.64; $z = 2.12$; $P = .03$) and a nonsignificant effect for both OCD ($g = 0.01$; 95% CI, −0.24 to 0.27; $z = 0.10$; $P = .92$) and PTSD ($g = 0.03$; 95% CI, −0.30 to 0.35; $z = 0.17$; $P = .87$). Follow-up

Figure 1. Study Selection and Rationale for Exclusion



Abbreviations: OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

Table 1. Characteristics of Randomized Controlled Trials of D-Cycloserine Augmented Exposure-Based Cognitive-Behavioral Therapy

Trial	N	Primary Diagnosis	Age, Mean, y	Male, %	Comorbid Depressive Disorders, %	Comorbid Anxiety Disorders, %	SRI, %	No. of Therapy Sessions	D-Cycloserine Dose Timing, h	No. of D-Cycloserine Doses	Analysis Type	Method Quality
Ressler et al[15]	27	SP	46	41	0	0	NR	2	–3	2	ITT	26
Hofmann et al[16]	32	SAD	34	67	15	33	33	5	–1	4	COMP	32
Storch et al[17]	24	OCD	29	50	38	75	50	12	–4	12	COMP	31
Kushner et al[18]	32	OCD	37	38	25	12.5	34.4	4	–2	4	ITT	31
Wilhelm et al[19]	23	OCD	39	61	26	43	39	10	–1	10	ITT	31
Guastella et al[20]	56	SAD	35	57	16	16	9	5	–1	4	ITT	36
Storch et al[21]	30	OCD	12	63	10	27	30	10	–1	7	ITT	36
Otto et al[22]	28	PD	37	50	17.9	28.6	54.5	5	–1	3	COMP	28
Litz et al[23]	26	PTSD	32	100	30.8	11.5	7.7	6	–1	4	ITT	36
de Kleine et al[24]	67	PTSD	38	19	54	42	25	8	–1	6	ITT	36
Nave et al[25]	20	SP	37	40	5	0	10	1	–1	1	COMP	30
Farrell et al[26]	17	OCD	13	41	12	59	76	9	–1	5	COMP	36
Rodebaugh et al[27]	34	SAD	43	33	47	47	35	1	0	2	COMP	32
Hofmann et al[28]	169	SAD	33	57	26.6	25.4	0	12	–1	5	ITT	38
Tart et al[29]	29	SP	33	24	34	66	0	2	1	2	ITT	35
Mataix-Coles et al[30]	27	OCD	15	52	11	48	26	14	1	10	ITT	34
Scheeringa and Weems[31]	57	PTSD	12	44	61.4	59.7	10.5	12	–1	7	ITT	38
Rothbaum et al[32]	106	PTSD	34	93	77.3	12.2	NR	6	–0.5	5	ITT	29
Difede et al[33]	25	PTSD	46	76	64	NR	NR	12	–1.5	10	ITT	35
Andersson et al[34]	128	OCD	35	42	9	25	24	12	–1	5	ITT	39

Abbreviations: COMP = completer analysis, ITT = intent-to-treat analysis, NR = not reported, OCD = obsessive-compulsive disorder, PD = panic disorder, PTSD = posttraumatic stress disorder, SAD = social anxiety disorder, SP = specific phobia.

comparisons found no significant difference between anxiety disorders and OCD ($P = .12$), anxiety disorders and PTSD ($P = .18$), or OCD and PTSD ($P = .95$).

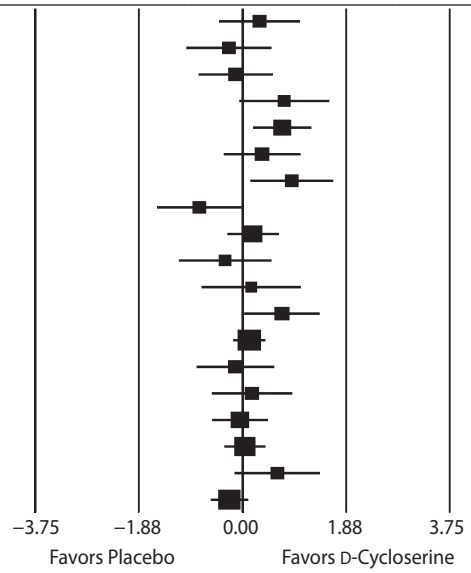
Acute treatment response. A random-effects meta-analysis found a nonsignificant effect for D-cycloserine–augmented relative to placebo-augmented treatment (RR = 1.08; 95% CI, 0.94 to 1.25; $z = 1.08$; $P = .28$), with significant heterogeneity ($Q_{15} = 35.45$, $P = .002$, $I^2 = 57.68\%$) (Figure 2). Visual inspection of the funnel plot and Egger test for bias indicated that publication bias was not present ($t = 0.03$, $P = .97$). When diagnostic groups were examined separately, there was a nonsignificant effect for anxiety disorders (RR = 1.12; 95% CI, 0.83 to 1.50; $z = 0.75$; $P = .45$), OCD (RR = 1.04; 95% CI, 0.91 to 1.18; $z = 0.51$; $P = .61$), and PTSD (RR = 1.07; 95% CI, 0.59 to 2.96; $z = 0.23$; $P = .82$). Follow-up comparisons found no significant difference between anxiety disorders and OCD ($P = .63$), anxiety disorders and PTSD ($P = .90$), or OCD and PTSD ($P = .91$).

Acute treatment remission. A random-effects meta-analysis found a nonsignificant effect for D-cycloserine–augmented relative to placebo-augmented treatment (RR = 1.09; 95% CI, 0.95 to 1.25; $z = 1.16$; $P = .25$), with minimal heterogeneity present ($Q_{12} = 13.33$, $P = .35$, $I^2 = 9.97\%$) (Figure 2). Visual inspection of the funnel plot and Egger test for bias indicated that publication bias was not significant ($t = 0.18$, $P = .86$). When diagnostic groups

Figure 2. Acute Treatment Efficacy (A), Treatment Response (B), and Diagnostic Remission (C) in D-Cycloserine or Placebo Augmentation Trials of Exposure-Based Treatment[a]

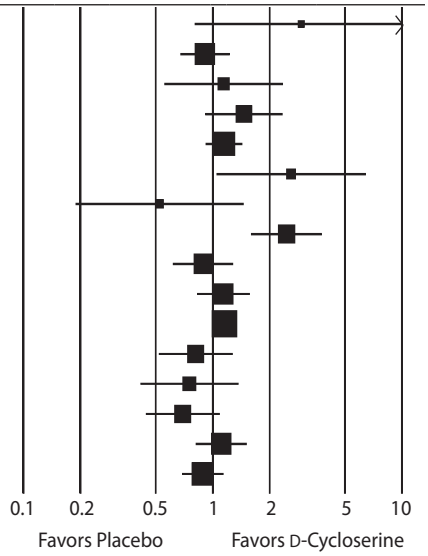
A. Acute Treatment Efficacy

Trial	Hedges *g*	Lower Limit	Upper Limit	*P* Value	Relative Weight
Hofmann et al, 2006[16]	0.31	−0.43	1.05	.415	4.06
Storch et al, 2007[17]	−0.25	−1.02	0.53	.535	3.79
Kushner et al, 2007[18]	−0.12	−0.80	0.56	.724	4.61
Wilhelm et al, 2008[19]	0.76	−0.07	1.58	.072	3.46
Guastella et al, 2008[20]	0.72	0.19	1.25	.008	6.28
Storch et al, 2010[21]	0.35	−0.35	1.06	.322	4.39
Otto et al, 2010[22]	0.89	0.13	1.65	.021	3.93
Litz et al, 2012[23]	−0.78	−1.55	−0.01	.048	3.80
de Kleine et al, 2012[24]	0.19	−0.28	0.66	.432	7.16
Nave et al, 2012[25]	−0.31	−1.16	0.53	.465	3.33
Farrell et al, 2013[26]	0.16	−0.75	1.06	.732	2.98
Rodebaugh et al, 2013[27]	0.71	0.03	1.40	.042	4.52
Hofmann et al, 2013[28]	0.12	−0.18	0.42	.419	10.49
Tart et al, 2013[29]	−0.13	−0.84	0.58	.725	4.33
Mataix-Coles et al, 2014[30]	0.17	−0.56	0.91	.645	4.12
Scheeringa and Weems, 2014[31]	−0.05	−0.56	0.47	.858	6.58
Rothbaum et al, 2014[32]	0.04	−0.33	0.42	.822	8.88
Difede et al, 2014[33]	0.63	−0.15	1.41	.114	3.77
Andersson et al, 2015[34]	−0.24	−0.58	0.11	.181	9.53



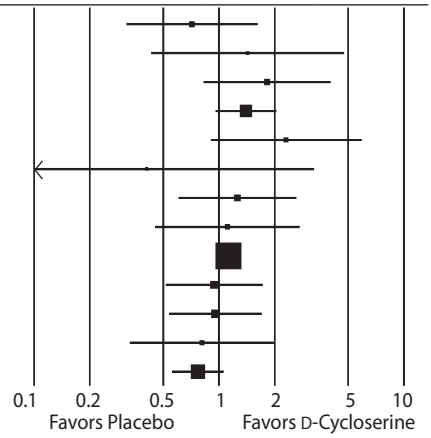
B. Acute Treatment Response

Trial	Risk Ratio	Lower Limit	Upper Limit	Relative Weight
Ressler et al, 2004[15]	2.94	0.80	10.81	1.13
Storch et al, 2007[17]	0.91	0.67	1.23	8.53
Kushner et al, 2007[18]	1.14	0.55	2.36	3.08
Wilhelm et al, 2008[19]	1.46	0.91	2.36	5.50
Storch et al, 2010[21]	1.15	0.91	1.44	10.24
Otto et al, 2010[22]	2.60	1.04	6.48	2.11
Litz et al, 2012[23]	0.52	0.19	1.46	1.73
de Kleine et al, 2012[24]	2.46	1.59	3.80	6.10
Nave et al, 2012[25]	0.89	0.61	1.29	7.18
Farrell et al, 2013[26]	1.14	0.82	1.58	8.11
Hofmann et al, 2013[28]	1.15	1.03	1.29	12.68
Tart et al, 2013[29]	0.81	0.52	1.28	5.84
Mataix-Coles et al, 2014[30]	0.75	0.41	1.38	4.05
Scheeringa and Weems, 2014[31]	0.70	0.44	1.10	5.82
Rothbaum et al, 2014[32]	1.11	0.81	1.52	8.30
Andersson et al, 2015[34]	0.89	0.69	1.15	9.60



C. Acute Diagnostic Remission

Trial	Risk Ratio	Lower Limit	Upper Limit	Relative Weight
Storch et al, 2007[17]	0.71	0.31	1.63	2.71
Kushner et al, 2007[18]	1.43	0.43	4.77	1.29
Wilhelm et al, 2008[19]	1.82	0.82	4.04	2.87
Storch et al, 2010[21]	1.40	0.95	2.05	11.06
Otto et al, 2010[22]	2.31	0.90	5.92	2.08
Litz et al, 2012[23]	0.41	0.05	3.28	0.44
de Kleine et al, 2012[24]	1.26	0.60	2.64	3.33
Farrell et al, 2013[26]	1.11	0.45	2.75	2.25
Hofmann et al, 2013[28]	1.13	1.00	1.27	47.28
Tart et al, 2013[29]	0.94	0.51	1.73	4.81
Mataix-Coles et al, 2014[30]	0.96	0.54	1.71	5.25
Rothbaum et al, 2014[32]	0.81	0.33	2.00	2.26
Andersson et al, 2015[34]	0.77	0.56	1.07	14.38

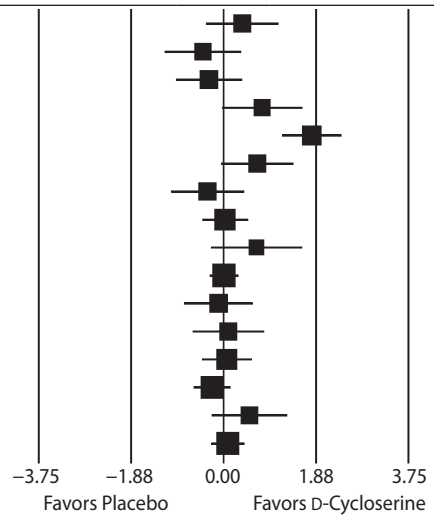


[a]Upper and lower limits in forest plots represent 95% CIs.

Figure 3. Follow-Up Treatment Efficacy (A), Treatment Response (B), and Diagnostic Remission (C) in D-Cycloserine or Placebo Augmentation Trials of Exposure-Based Treatment[a]

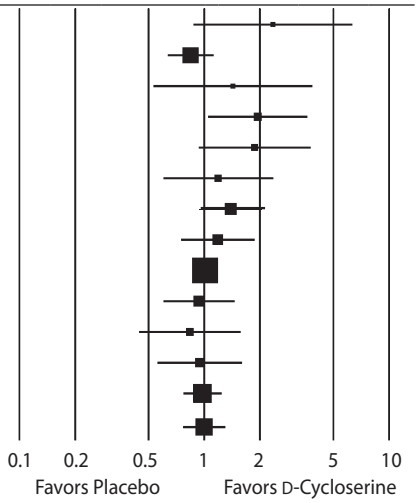
A. Follow-Up Treatment Efficacy

Trial	Hedges *g*	Lower Limit	Upper Limit	Relative Weight
Hofmann et al, 2006[16]	0.38	−0.36	1.12	5.43
Storch et al, 2007[17]	−0.42	−1.20	0.36	5.17
Kushner et al, 2007[18]	−0.30	−0.98	0.39	5.87
Wilhelm et al, 2008[19]	0.78	−0.04	1.61	4.88
Guastella et al, 2008[20]	1.79	1.17	2.40	6.39
Otto et al, 2010[22]	0.68	−0.06	1.42	5.43
Litz et al, 2012[23]	−0.33	−1.08	0.42	5.38
de Kleine et al, 2012[24]	0.03	−0.44	0.51	7.56
Farrell et al, 2013[26]	0.67	−0.26	1.60	4.27
Hofmann et al, 2013[28]	0.01	−0.29	0.31	9.00
Tart et al, 2013[29]	−0.10	−0.81	0.61	5.67
Mataix-Coles et al, 2014[30]	0.10	−0.64	0.83	5.50
Scheeringa and Weems, 2014[31]	0.07	−0.44	0.58	7.23
Rothbaum et al, 2014[32]	−0.23	−0.61	0.15	8.36
Difede et al, 2014[33]	0.52	−0.25	1.30	5.23
Andersson et al, 2015[34]	0.09	−0.26	0.43	8.65



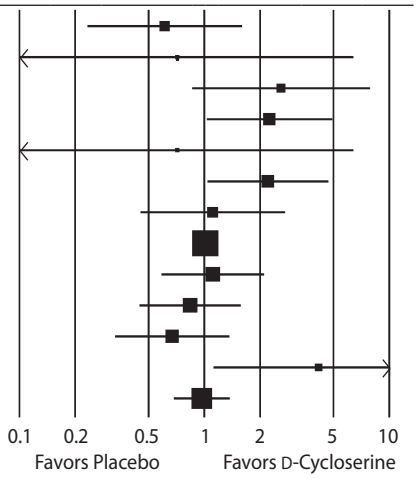
B. Follow-Up Treatment Response

Trial	Risk Ratio	Lower Limit	Upper Limit	Relative Weight
Ressler et al, 2004[15]	2.35	0.87	6.37	1.19
Storch et al, 2007[17]	0.84	0.63	1.13	11.20
Kushner et al, 2007[18]	1.43	0.53	3.86	1.20
Wilhelm et al, 2008[19]	1.95	1.05	3.63	2.95
Otto et al, 2010[22]	1.88	0.93	3.78	2.35
Litz et al, 2012[23]	1.19	0.60	2.37	2.43
de Kleine et al, 2012[24]	1.39	0.93	2.09	6.46
Farrell et al, 2013[26]	1.19	0.75	1.88	5.11
Hofmann et al, 2013[28]	1.01	0.88	1.17	27.75
Tart et al, 2013[29]	0.94	0.60	1.47	5.35
Mataix-Coles et al, 2014[30]	0.84	0.44	1.58	2.82
Scheeringa and Weems, 2014[31]	0.95	0.56	1.61	3.95
Rothbaum et al, 2014[32]	0.98	0.77	1.25	14.62
Andersson et al, 2015[34]	1.00	0.76	1.31	12.63



C. Follow-Up Diagnostic Remission

Trial	Risk Ratio	Lower Limit	Upper Limit	Relative Weight
Storch et al, 2007[17]	0.61	0.23	1.60	4.54
Kushner et al, 2007[18]	0.71	0.08	6.43	0.99
Wilhelm et al, 2008[19]	2.60	0.85	7.92	3.54
Otto et al, 2010[22]	2.25	1.02	4.94	6.35
Litz et al, 2012[23]	0.71	0.08	6.43	0.99
de Kleine et al, 2012[24]	2.21	1.03	4.71	6.72
Farrell et al, 2013[26]	1.11	0.45	2.75	5.04
Hofmann et al, 2013[28]	1.01	0.88	1.17	27.20
Tart et al, 2013[29]	1.11	0.58	2.12	8.57
Mataix-Coles et al, 2014[30]	0.84	0.44	1.58	8.73
Rothbaum et al, 2014[32]	0.67	0.33	1.37	7.38
Difede et al, 2014[33]	4.15	1.11	15.49	2.62
Andersson et al, 2015[34]	0.97	0.68	1.38	17.31



[a]Upper and lower limits in forest plots represent 95% CIs.

were examined separately, there was a nonsignificant effect for anxiety disorders (RR = 1.15; 95% CI, 0.89 to 1.50; $z = 1.06$; $P = .29$), OCD (RR = 1.09; 95% CI, 0.80 to 1.38; $z = 0.38$; $P = .71$), and PTSD (RR = 0.99; 95% CI, 0.57 to 1.71; $z = -0.05$; $P = .96$). Follow-up comparisons found no significant difference between anxiety disorders and OCD ($P = .64$), anxiety disorders and PTSD ($P = .62$), or OCD and PTSD ($P = .84$).

Follow-up efficacy. A random-effects meta-analysis found a nonsignificant effect for D-cycloserine–augmented relative to placebo-augmented treatment ($g = 0.21$; 95% CI, −0.05 to 0.46; $z = 1.60$; $P = .11$) (Figure 3). Visual inspection of the forest plot, Q statistic, and I^2 statistic identified significant heterogeneity ($Q_{15} = 44.94$, $P < .001$, $I^2 = 66.62\%$). Visual inspection of the funnel plot and Egger test for bias indicated that publication bias was not significant ($t = 1.24$, $P = .23$). When diagnostic groups were examined separately, there was a nonsignificant effect for anxiety disorders ($g = 0.54$; 95% CI, −0.15 to 1.24; $z = 1.53$; $P = .13$), OCD ($g = 0.10$; 95% CI, −0.22 to 0.42; $z = 0.62$; $P = .53$), and PTSD ($g = -0.05$; 95% CI, −0.28 to 0.18; $z = -0.42$; $P = .68$). Follow-up comparisons found no significant difference between anxiety disorders and OCD ($P = .26$), anxiety disorders and PTSD ($P = .11$), or OCD and PTSD ($P = .45$).

Follow-up treatment response. A random-effects meta-analysis found a nonsignificant effect for D-cycloserine–augmented relative to placebo-augmented treatment (RR = 1.06; 95% CI, 0.95 to 1.18; $z = 0.96$; $P = 0.34$), with some heterogeneity present ($Q_{13} = 15.33$, $P = .23$, $I^2 = 15.21\%$) (Figure 3). Visual inspection of the funnel plot and Egger test for bias suggested that publication bias existed ($t = 2.25$, $P = .04$). A trim-and-fill method was applied, and 3 studies were trimmed, which produced a revised summary effect that was also nonsignificant (RR = 1.02; 95% CI, 0.87 to 1.16). When diagnostic groups were examined separately, there was a nonsignificant effect for anxiety disorders (RR = 1.17; 95% CI, 0.85 to 1.61; $z = 0.97$; $P = .33$), OCD (RR = 1.04; 95% CI, 0.84 to 1.30; $z = 0.39$; $P = .69$), and PTSD (RR = 1.07; 95% CI, 0.88 to 1.28; $z = 0.66$; $P = .51$). Follow-up comparisons found no significant difference between anxiety disorders and OCD ($P = .56$), anxiety disorders and PTSD ($P = .62$), or OCD and PTSD ($P = .89$).

Follow-up diagnostic remission. A random-effects meta-analysis found a nonsignificant effect for D-cycloserine–augmented relative to placebo-augmented treatment (RR = 1.12; 95% CI, 0.90 to 1.40; $z = 1.01$; $P = .32$), with moderate heterogeneity ($Q_{12} = 17.96$, $P = .12$, $I^2 = 33.20\%$) (Figure 3). Visual inspection of the funnel plot and Egger test for bias suggested that publication bias was not significant ($t = 1.07$, $P = .31$). When diagnostic groups were examined separately, there was a nonsignificant effect for anxiety disorders (RR = 1.20; 95% CI, 0.81 to 1.77; $z = 0.89$; $P = .38$), OCD (RR = 0.97; 95% CI, 0.74 to 1.27; $z = -0.21$; $P = .84$), and PTSD (RR = 1.49; 95% CI, 0.61 to 3.65; $z = 0.87$; $P = .38$). Follow-up comparisons found no significant difference between anxiety disorders and OCD ($P = .40$), anxiety disorders and PTSD ($P = .66$), or OCD and PTSD ($P = .37$).

Moderators of D-Cycloserine–Augmented Treatment

Table 2 presents treatment moderators examined across D-cycloserine augmentation trials for both acute and follow-up treatment efficacy, treatment response, and symptom remission.

Acute outcomes. Across studies, trials published earlier were associated with larger RR for diagnostic remission (see Table 2). There were no other significant moderators across the full sample of trials for acute treatment efficacy, response, or remission.

When diagnostic groups were examined separately, larger D-cycloserine effects on treatment efficacy were associated with a greater percentage of participants taking SRI medications in anxiety disorder trials (7 studies) ($B = 0.01$, SE = 0.01, $z = 2.02$, $P = .04$) and a greater percentage of male participants in OCD trials (7 studies) ($B = 0.03$, SE = 0.01, $z = 2.08$, $P = .04$). No moderators of acute treatment efficacy were found for PTSD.

In terms of acute treatment response, larger D-cycloserine effects were associated with a greater percentage of participants on SRI medications in PTSD trials (4 studies) ($B = 0.09$, SE = 0.02, $z = 4.29$, $P < .001$), while no significant moderators emerged for anxiety disorders or OCD.

Although no moderators of acute diagnostic remission were identified for anxiety or PTSD trials, multiple moderators were identified for OCD trials (7 studies). Larger D-cycloserine treatment effects were associated with a greater percentage of male participants ($B = 0.03$, SE = 0.01, $z = 2.32$, $P = .02$), while smaller D-cycloserine effects were associated with larger sample sizes ($B \leq -0.01$, SE ≤ 0.01, $z = -2.14$, $P = .03$) and more recent publications ($B = -0.07$, SE = 0.04, $z = -2.02$, $P = .04$).

Follow-up outcomes. No significant moderators were identified across trials for treatment efficacy, response, or remission at initial follow-up (see Table 2).

When diagnostic groups were examined separately, larger D-cycloserine effects on treatment efficacy were associated with greater participant mean age for anxiety disorders (5 studies) ($B = 0.56$, SE = 0.21, $z = 2.71$, $P = .007$). No moderators of treatment efficacy at follow-up were found for OCD or PTSD.

In terms of follow-up treatment response, larger D-cycloserine effects were associated with greater participant mean age for anxiety disorders (5 studies) ($B = 0.07$, SE = 0.04, $z = 1.96$, $P = .05$). However, smaller D-cycloserine effects were associated with greater co-occurring depressive disorders ($B = -0.03$, SE = 0.02, $z = -2.10$, $P = .04$), greater methodological quality ($B = -0.06$, SE = 0.03, $z = 2.10$, $P = .04$), and more recently published studies ($B = -0.11$, SE = 0.05, $z = -2.19$, $P = .03$) for anxiety disorders. No moderators of treatment response were found for OCD or PTSD.

Although no moderators of diagnostic remission at follow-up were identified for OCD trials, multiple moderators were identified for both anxiety disorders (3 studies) and PTSD (4 studies). Larger D-cycloserine effects were associated with greater mean participant age ($B = 0.33$, SE = 0.17, $z = 1.96$, $P = .05$) and percentage of participants

Table 2. Regression Analyses and Analog to ANOVA Examining Moderators of Treatment Efficacy, Treatment Response, and Remission for D-Cycloserine–Augmented Cognitive-Behavioral Trials

	Treatment Efficacy (n = 19)				Treatment Response (n = 16)				Diagnostic Remission (n = 13)			
Study Characteristic	*B*	SE	*z*	*P*	*B*	SE	*z*	*P*	*B*	SE	*z*	*P*
Sample size	< −0.01	< 0.01	−0.83	.41	< 0.01	< 0.01	0.13	.90	< −0.01	< 0.01	−0.73	.46
Percentage male	< −0.01	< 0.01	−0.29	.77	< −0.01	< 0.01	−0.80	.42	< 0.01	0.01	0.48	.63
Mean participant age	0.01	0.01	0.87	.38	0.01	0.01	1.49	.14	−0.01	0.01	−0.60	.55
Percent comorbid depressive disorders	< 0.01	< 0.01	0.03	.97	< 0.01	< 0.01	0.27	.79	< −0.01	< 0.01	−0.14	.89
Percent comorbid anxiety disorders	< 0.01	< 0.01	0.29	.77	< −0.01	< 0.01	−0.67	.50	< −0.01	< 0.01	−0.40	.69
Percentage of patients on SRI medication	0.01	0.01	1.20	.23	< 0.01	< 0.01	1.11	.27	< 0.01	< 0.01	0.58	.56
No. of therapy sessions	−0.01	0.02	−0.57	.57	−0.01	0.02	−0.57	.57	−0.02	0.03	−0.66	.51
Time of D-cycloserine administration	0.06	0.10	0.59	.55	−0.03	0.07	−0.52	.61	< 0.01	0.09	0.02	.98
No. of D-cycloserine doses	0.01	0.04	0.26	.79	< −0.01	0.03	−0.19	.85	< 0.01	0.04	0.07	.95
Publication year	−0.04	0.03	−1.39	.17	−0.04	0.03	−1.45	.15	−0.07	0.03	−2.11	.04
Methodological quality rating	−0.03	0.03	−1.06	.29	−0.02	0.02	−1.00	.32	−0.03	0.03	−1.10	.27
		Q	*df*	*P*		*Q*	*df*	*P*		*Q*	*df*	*P*
Primary diagnostic classification		2.80	2	.25		0.24	2	.89		0.36	2	.84
Child versus adult		0.03	1	.86		0.83	1	.36		0.81	1	.37
Analysis type (ITT/COMP)		0.62	1	.43		0.05	1	.82		0.07	1	.79
	Follow-Up Treatment Efficacy (n = 16)				Follow-Up Treatment Response (n = 14)				Follow-Up Diagnostic Remission (n = 13)			
	B	SE	*z*	*P*	*B*	SE	*z*	*P*	*B*	SE	*z*	*P*
Sample size	< −0.01	< 0.01	−0.74	.46	< −0.01	< 0.01	−0.80	.42	< −0.01	< 0.01	−1.07	.29
Percentage male	< −0.01	0.01	−0.11	.91	< −0.01	< 0.01	−0.59	.55	−0.01	0.01	−0.96	.34
Mean participant age	0.01	0.02	0.42	.67	0.01	0.01	1.32	.19	0.03	0.01	1.70	.09
Percent comorbid depressive disorders	−0.01	0.01	−1.45	.15	< −0.01	< 0.01	−0.66	.51	< 0.01	0.01	0.32	.75
Percent comorbid anxiety disorders	< −0.01	0.01	−0.47	.64	< −0.01	< 0.01	−0.96	.34	< 0.01	0.01	0.26	.80
Percentage of patients on SRI medication	< 0.01	0.01	0.42	.67	< 0.01	< 0.01	0.70	.48	< 0.01	< 0.01	0.82	.41
No. of therapy visits	−0.02	0.04	−0.48	.63	−0.02	0.02	−1.33	.18	−0.02	0.03	−0.73	.47
Time of D-cycloserine administration	0.05	0.13	0.40	.69	0.01	0.05	0.26	.79	< −0.01	0.11	−0.01	.99
No. of D-cycloserine doses	−0.02	0.05	−0.33	.74	−0.02	0.02	−1.02	.31	< −0.01	0.05	−0.10	.92
Publication year	−0.05	0.04	−1.21	.23	−0.02	0.02	−1.02	.31	−0.05	0.05	−0.88	.38
Methodological quality rating	0.01	0.04	0.23	.82	−0.01	0.02	−0.72	.47	−0.01	0.03	−0.43	.67
Follow-up duration	−0.13	0.10	−1.31	.19	< −0.01	0.07	−0.05	.96	0.08	0.11	0.71	.48
		Q	*df*	*P*		*Q*	*df*	*P*		*Q*	*df*	*P*
Primary diagnostic classification		2.73	2	.26		0.36	2	.84		1.31	2	.52
Child versus adult		0.01	1	.92		0.13	1	.72		0.68	1	.41
Analysis type (ITT/COMP)		0.22	1	.64		0.10	1	.75		0.06	1	.81

Abbreviations: ANOVA = analysis of variance, COMP = completer analysis, ITT = intention to treat.

on an SRI medication ($B = 0.01$, SE = 0.01, $z = 1.95$, $P = .05$), whereas smaller D-cycloserine effects were associated with greater methodological quality ($B = -0.07$, SE = 0.04, $z = -1.92$, $P = .05$) and more recently published studies ($B = -0.26$, SE = 0.14, $z = -1.95$, $P = .05$) in anxiety disorder trials. Additionally, intent-to-treat studies (RR = 1.02) had smaller D-cycloserine effects relative to completer analyses among anxiety disorder trials (RR = 2.25) ($Q_1 = 3.80$, $P = .05$). For PTSD trials, greater D-cycloserine treatment effects were associated with a greater percentage of co-occurring anxiety disorders ($B = 0.04$, SE = 0.02, $z = 2.28$, $P = .02$), more therapy sessions ($B = 0.33$, SE = 0.12, $z = 2.66$, $P = .007$), earlier D-cycloserine dosing ($B = -1.91$, SE = 0.70, $z = -2.73$, $P = .006$), more D-cycloserine doses ($B = 0.33$, SE = 0.16, $z = 2.04$, $P = .04$), and greater methodological quality ($B = 0.17$, SE = 0.09, $z = 1.93$, $P = .05$).

DISCUSSION

This study evaluated treatment efficacy, response, and diagnostic remission of D-cycloserine–augmented treatment for anxiety disorders, OCD, and PTSD during acute treatment and at follow-up assessments using validated ratings. While prior meta-analyses have provided initial support for D-cycloserine, this meta-analysis addressed several limitations of prior investigations, such as small sample size,[36] use of psychometrically validated rating scales to calculate effects,[10,36] and limited examination of moderators[37,38] across 3 clinically relevant measures of therapeutic outcome. Moreover, this study completed an extensive examination of theoretically derived treatment moderators across outcomes. Findings suggest minimal benefit of D-cycloserine relative to placebo augmentation across all 3 outcomes, with the most robust effect observed among anxiety disorders during acute treatment ($g = 0.33$). This finding may be understood in several ways. First, the minimal effect of D-cycloserine across trials may be attributed to the robust effect sizes of existing exposure-based treatments in which there is limited room for improvement. Second, as D-cycloserine can influence memory reconsolidation,[56] conditions that have more fear-based psychopathology and well-defined exposure targets (eg, public speaking, specific phobias) may enable better fear-memory reconsolidation in treatment. Conversely, conditions that have greater heterogeneity, such as OCD,

may be influenced by sample-dependent characteristics of symptom presentation (eg, fear-based symptoms versus not-just-right symptoms). Third, given the potential importance of between- and within-session habituation,[32,57] anxiety disorders may allow for better habituation within the session due to contained triggers. Meanwhile, from an inhibitory learning model perspective,[58] it may be that within-session habituation serves as a possible marker that the prior fear association is adequately inhibited and fear extinction associations are strengthened. Given the contained nature of anxiety triggers predominantly studied in D-cycloserine trials (eg, social anxiety disorder, specific phobias), this may be more easily achieved for anxiety disorders relative to conditions that have more expansive triggers like OCD and PTSD. Fourth, as OCD and PTSD often have greater psychiatric comorbidities,[2,3] it may be that specific co-occurring conditions impede extinction learning targeted in treatment. While D-cycloserine augmentation can provide some enhancement of outcomes beyond placebo, further research is needed to clarify mechanisms and disentangle its effect across disorders.

When treatment moderators were examined, a greater percentage of participants taking SRI medications was associated with greater D-cycloserine effects during acute treatment for anxiety disorders and PTSD. This finding is consistent with animal research suggesting synergy between antidepressant drugs and fear extinction.[41] Although it is different than the finding of an attenuated response with SRI medication in adults with OCD,[34] SRI medications can reduce negative biases in information processing hypothesized to play a central role in fear-based psychopathology.[59,60] Thus, SRIs may indirectly strengthen the appropriate formation of fear extinction learning that occurs with treatment. Conversely, other animal model studies (eg, Burghardt et al[42]) suggest that the chronic use of antidepressants may impede fear extinction. Thus, it may be that SRI medications may be interacting with brain-derived neurotrophic factor (BDNF) to enhance synaptic plasticity of fear extinction targeted by D-cycloserine in exposure-based treatments.[61] Among OCD trials, a greater percentage of male participants was associated with larger D-cycloserine effects in acute treatment. Although this suggests a possible gender difference in D-cycloserine response, it may also be attributed to tic-related OCD that has a greater male preponderance.[62] Indeed, tic-related OCD serves a *DSM* specifier and has been suggested to be phenomenologically distinct from OCD without tics, with a differential treatment response profile.[1,62] Additionally, a larger sample size and more recently published studies were associated with smaller D-cycloserine effects in OCD trials, suggesting that D-cycloserine's broad benefit diminishes in larger studies. As OCD has a heterogeneous presentation, subtype analyses may prove useful in clarifying whether specific OCD symptom dimensions respond better to D-cycloserine augmentation (eg, fear-based symptoms versus not-just-right symptoms).

When examining moderators at initial follow-up assessments, a greater average participant age and percentage of participants on SRI medications was associated with larger D-cycloserine benefit for anxiety disorders. Meanwhile, greater depressive disorder, methodological quality, and recently published studies were associated with reduced D-cycloserine effects. While reduced effects for methodological quality and publication year may be anticipated, greater co-occurring depressive disorders may interfere with extinction learning targeted in treatment.[63] It would be interesting to examine whether co-occurring depression moderated D-cycloserine effects among anxiety disorder trials with patient-level data. Among PTSD trials, a greater percentage of anxiety disorders, treatment sessions, and D-cycloserine doses were associated with greater D-cycloserine effects. As greater co-occurring anxiety disorders may be associated with greater fear-based psychopathology, this may provide further evidence for D-cycloserine's benefit in extinction augmentation of fear-based psychopathology. Notably, extinction enhancement may not necessarily yield treatment enhancement, especially for symptoms not directly tied to fear. While the positive association between D-cycloserine effects and more treatment sessions makes clinical sense, the findings regarding a positive association with more D-cycloserine doses is somewhat counterintuitive based on the literature.[10] This particular effect may be attributed to the robust results in diagnostic remission that occurred at follow-up in a trial that had the highest D-cycloserine doses.[33]

Several limitations should be considered when interpreting these findings. First, there was inconsistent reporting of variables needed to calculate treatment efficacy, response, and diagnostic remission. Although study investigators were contacted to obtain these data, this resulted in different studies being included for different outcomes. Second, while this evaluation emphasized the importance of standardized rating scales, it is important to note that these studies focused on acute outcomes (often in truncated treatment protocols) and were not designed with the goal of diagnostic remission. Third, this evaluation examined 3 outcomes across multiple study characteristics across and within psychiatric conditions. This raises some concerns related to familywise error. While theoretically derived moderators were selected for analysis, caution in interpreting these findings as definitive is warranted. Fourth, this study was well powered to detect treatment moderators across trials, but had modest power to detect treatment moderators within disorders.[55] As such, nonsignificant moderators should not be interpreted as a conclusive lack of association within conditions. Future research should examine identified treatment moderators in patient-level data to confirm these findings.[64] Finally, there were limited characteristics available for extraction across RCTs. Thus, there may be unexamined factors such as within- and between-session habituation that could influence D-cycloserine effects.[32,57]

In summary, these meta-analytic findings suggest that D-cycloserine augmentation yields a small-to-moderate albeit nonsignificant benefit across disorders, with treatment moderators varying across conditions. These findings highlight 3 directions for future research. First,

the heterogeneous findings across RCTs highlight the importance of preclinical research on cognitive enhancers. As human RCTs are complicated by the interaction of pharmacologic agents, human behavior, co-occurring conditions, and treatment protocols, preclinical research in animals can prove useful to elucidate possible biomarkers of D-cycloserine response (eg, BDNF levels, SRI medications). This line of research may be useful to clarify whether SRI medications potentiate or impede D-cycloserine treatment response and better understand individualized responses to cognitive enhancers. Second, further research is needed to understand D-cycloserine's mechanism of action in humans. For instance, recent research suggests that D-cycloserine enhances fear extinction in specific phobias via mechanisms of generalization and context learning.[65] Additionally, an ongoing trial aims to further evaluate the dose-timing aspect of D-cycloserine and will also explore a biological marker of fear conditioning in adults with anxiety disorders.[66] While these 2 studies are noteworthy, considerably more well-designed studies are needed to evaluate its mechanisms in humans; such studies should include idiographic patient factors, therapy-specific reactions, and phenotypes rather than broad demographic stratifications.[67] Additionally, when considering study designs, accounting for identified treatment moderators in the design process (eg, stratifying randomization by SRI medication status) may be useful. Finally, the present findings regarding disorder-specific moderation support the importance of treatment moderators as a source of important information to individualize and/or maximize the augmentative benefit of D-cycloserine in fear-based psychopathology. Future work employing patient-level analyses within large RCTs and/or aggregating data from similarly designed RCTs within specific disorders may be helpful in furthering our understanding in this area.

Submitted: August 18, 2015; accepted November 2, 2015.

Online first: June 7, 2016.

Potential conflicts of interest: **Dr McGuire** receives support from the Tourette Association of American and the National Institute of Mental Health (NIMH) through T32MH073517. **Dr Piacentini** has received support from his work from NIMH, Tourette Syndrome Association, Pfizer, and Pettit Family Foundation; has received book royalties from Oxford University Press and Guilford Publications; and has received speaking honoraria from the Tourette Syndrome Association, International OCD Foundation (IOCDF), and Trichotillomania Learning Center. **Dr McCracken** has received grant or research support from National Institutes of Health (NIH), Seaside Therapeutics, Roche, and Otsuka; and has served as a consultant to BioMarin and PharmaNet. **Dr Storch** has received support from the NIH, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, IOCDF, and Ortho-McNeil Scientific Affairs; receives textbook honorarium from Springer publishers, American Psychological Association, Lawrence Erlbaum, and Wiley-Blackwell; is a consultant for Prophase and Rogers Memorial Hospital; is on the speakers bureau and scientific advisory board for the IOCDF; and receives research support from the All Children's Hospital Guild Endowed Chair. **Ms Wu** reports no relevant financial disclosures.

Funding/support: None.

Disclaimer: The views expressed within this article represent those of the authors.

Acknowledgments: The authors express their appreciation to the study investigators for their responsiveness and/or assistance in obtaining data not published in their original article.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Publishing; 2013.
2. Ruscio AM, Stein DJ, Chiu WT, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15(1):53–63.
3. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617–627.
4. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.
5. Myers KM, Davis M. Mechanisms of fear extinction. *Mol Psychiatry*. 2007;12(2):120–150.
6. Olatunji BO, Cisler JM, Deacon BJ. Efficacy of cognitive behavioral therapy for anxiety disorders: a review of meta-analytic findings. *Psychiatr Clin North Am*. 2010;33(3):557–577.
7. Deacon BJ, Farrell NR, Kemp JJ, et al. Assessing therapist reservations about exposure therapy for anxiety disorders: the Therapist Beliefs about Exposure Scale. *J Anxiety Disord*. 2013;27(8):772–780.
8. McGuire JF, Lewin AB, Storch EA. Enhancing exposure therapy for anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder. *Expert Rev Neurother*. 2014;14(8):893–910.
9. Singewald N, Schmuckermair C, Whittle N, et al. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacol Ther*. 2015;149:150–190.
10. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry*. 2008;63(12):1118–1126.
11. Fitzgerald PJ, Seemann JR, Maren S. Can fear extinction be enhanced? a review of pharmacological and behavioral findings. *Brain Res Bull*. 2014;105:46–60.
12. Ledgerwood L, Richardson R, Cranney J. D-cycloserine and the facilitation of extinction of conditioned fear: consequences for reinstatement. *Behav Neurosci*. 2004;118(3):505–513.
13. Rothbaum BO. Critical parameters for D-cycloserine enhancement of cognitive-behaviorial therapy for obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165(3):293–296.
14. Kalisch R, Holt B, Petrovic P, et al. The NMDA agonist D-cycloserine facilitates fear memory consolidation in humans. *Cereb Cortex*. 2009;19(1):187–196.
15. Ressler KJ, Rothbaum BO, Tannenbaum L, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry*. 2004;61(11):1136–1144.
16. Hofmann SG, Meuret AE, Smits JA, et al. Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Arch Gen Psychiatry*. 2006;63(3):298–304.
17. Storch EA, Merlo LJ, Bengtson M, et al. D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2007;22(4):230–237.
18. Kushner MG, Kim SW, Donahue C, et al. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry*. 2007;62(8):835–838.
19. Wilhelm S, Buhlmann U, Tolin DF, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry*. 2008;165(3):335–341, quiz 409.
20. Guastella AJ, Richardson R, Lovibond PF, et al. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biol Psychiatry*. 2008;63(6):544–549.
21. Storch EA, Murphy TK, Goodman WK, et al. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biol Psychiatry*. 2010;68(11):1073–1076.
22. Otto MW, Tolin DF, Simon NM, et al. Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biol Psychiatry*. 2010;67(4):365–370.
23. Litz BT, Salters-Pedneault K, Steenkamp MM, et al. A randomized placebo-controlled trial of D-cycloserine and exposure therapy for posttraumatic stress disorder. *J Psychiatr Res*. 2012;46(9):1184–1190.
24. de Kleine RA, Hendriks G-J, Kusters WJ, et al. A randomized placebo-controlled trial of D-cycloserine to enhance exposure therapy for posttraumatic stress disorder. *Biol Psychiatry*. 2012;71(11):962–968.
25. Nave AM, Tolin DF, Stevens MC. Exposure therapy, D-cycloserine, and functional magnetic resonance imaging in patients with snake phobia: a randomized pilot study. *J Clin Psychiatry*. 2012;73(9):1179–1186.
26. Farrell LJ, Waters AM, Boschen MJ, et al. Difficult-to-treat pediatric obsessive-compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-cycloserine-augmented behavior therapy. *Depress Anxiety*. 2013;30(8):723–731.
27. Rodebaugh TL, Levinson CA, Lenze EJ. A high-throughput clinical assay for testing drug facilitation of exposure therapy. *Depress*

Anxiety. 2013;30(7):631–637.
28. Hofmann SG, Smits JA, Rosenfield D, et al. D-Cycloserine as an augmentation strategy with cognitive-behavioral therapy for social anxiety disorder. *Am J Psychiatry*. 2013;170(7):751–758.
29. Tart CD, Handelsman PR, Deboer LB, et al. Augmentation of exposure therapy with post-session administration of D-cycloserine. *J Psychiatr Res*. 2013;47(2):168–174.
30. Mataix-Cols D, Turner C, Monzani B, et al. Cognitive-behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive-compulsive disorder: pilot randomised controlled trial. *Br J Psychiatry*. 2014;204(1):77–78.
31. Scheeringa MS, Weems CF. Randomized placebo-controlled D-cycloserine with cognitive behavior therapy for pediatric posttraumatic stress. *J Child Adolesc Psychopharmacol*. 2014;24(2):69–77.
32. Rothbaum BO, Price M, Jovanovic T, et al. A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. *Am J Psychiatry*. 2014;171(6):640–648.
33. Difede J, Cukor J, Wyka K, et al. D-cycloserine augmentation of exposure therapy for post-traumatic stress disorder: a pilot randomized clinical trial. *Neuropsychopharmacology*. 2014;39(5):1052–1058.
34. Andersson E, Hedman E, Enander J, et al. D-cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(7):659–667.
35. Murad MH, Montori VM. Synthesizing evidence: shifting the focus from individual studies to the body of evidence. *JAMA*. 2013;309(21):2217–2218.
36. Bontempo MA, Panza MKE, Bloch MH. D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders: a meta-analysis. *J Clin Psychiatry*. 2012;73(4):533–537.
37. Rodrigues H, Figueira I, Lopes A, et al. Does D-cycloserine enhance exposure therapy for anxiety disorders in humans? a meta-analysis. *PLoS ONE*. 2014;9(7):e93519.
38. Ori R, Amos T, Bergman H, et al. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. *Cochrane Database Syst Rev*. 2015;5:CD007803.
39. Britton JC, Grillon C, Lissek S, et al. Response to learned threat: an FMRI study in adolescent and adult anxiety. *Am J Psychiatry*. 2013;170(10):1195–1204.
40. Otto MW, Moshier SJ, Kinner DG, et al. De novo fear conditioning across diagnostic groups in the affective disorders: evidence for learning impairments. *Behav Ther*. 2014;45(5):619–629.
41. Karpova NN, Pickenhagen A, Lindholm J, et al. Fear erasure in mice requires synergy between antidepressant drugs and extinction training. *Science*. 2011;334(6063):1731–1734.
42. Burghardt NS, Sigurdsson T, Gorman JM, et al. Chronic antidepressant treatment impairs the acquisition of fear extinction. *Biol Psychiatry*. 2013;73(11):1078–1086.
43. Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. *Behav Neurosci*. 2003;117(2):341–349.
44. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
45. Bandelow B, Baldwin DS, Dolberg OT, et al. What is the threshold for symptomatic response and remission for major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder? *J Clin Psychiatry*. 2006;67(9):1428–1434.
46. Storch EA, Lewin AB, De Nadai AS, et al. Defining treatment response and remission in obsessive-compulsive disorder: a signal detection analysis of the Children's Yale-Brown Obsessive Compulsive Scale. *J Am Acad Child Adolesc Psychiatry*. 2010;49(7):708–717.
47. Lewin AB, De Nadai AS, Park J, et al. Refining clinical judgment of treatment outcome in obsessive-compulsive disorder. *Psychiatry Res*. 2011;185(3):394–401.
48. Schnurr PP, Friedman MJ, Engel CC, et al. Cognitive behavioral therapy for posttraumatic stress disorder in women: a randomized controlled trial. *JAMA*. 2007;297(8):820–830.
49. Weathers FW, Keane TM, Davidson JR. Clinician-Administered PTSD Scale: a review of the first ten years of research. *Depress Anxiety*. 2001;13(3):132–156.
50. Tolin DF, Abramowitz JS, Diefenbach GJ. Defining response in clinical trials for obsessive-compulsive disorder: a signal detection analysis of the Yale-Brown Obsessive Compulsive Scale. *J Clin Psychiatry*. 2005;66(12):1549–1557.
51. Moncrieff J, Churchill R, Drummond DC, et al. Development of a quality assessment instrument for trials of treatments for depression and neurosis. *Int J Methods Psychiatr Res*. 2001;10(3):126–133.
52. McGuire JF, Piacentini J, Lewin AB, et al. A meta-analysis of cognitive behavior therapy and medication for child obsessive compulsive disorder: moderators of treatment efficacy, response, and remission. *Depress Anxiety*. 2015;32(8):580–593.
53. Borenstein M, Hedges L, Higgins J, et al. *Comprehensive Meta-analysis*, 2nd ed [computer program]. Englewood, NJ: Biostat; 2005.
54. McGough JJ, Faraone SV. Estimating the size of treatment effects: moving beyond p values. *Psychiatry (Edgmont)*. 2009;6(10):21–29.
55. Borenstein M, Hedges LV, Higgins JPT, et al. *Introduction to Meta-Analysis*. Chichester, UK: John Wiley & Sons Ltd; 2009.
56. Lee JL, Gardner RJ, Butler VJ, et al. D-cycloserine potentiates the reconsolidation of cocaine-associated memories. *Learn Mem*. 2009;16(1):82–85.
57. Smits JA, Rosenfield D, Otto MW, et al. D-cycloserine enhancement of fear extinction is specific to successful exposure sessions: evidence from the treatment of height phobia. *Biol Psychiatry*. 2013;73(11):1054–1058.
58. Craske MG, Treanor M, Conway CC, et al. Maximizing exposure therapy: an inhibitory learning approach. *Behav Res Ther*. 2014;58:10–23.
59. Harmer CJ, Shelley NC, Cowen PJ, et al. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. *Am J Psychiatry*. 2004;161(7):1256–1263.
60. Cisler JM, Koster EH. Mechanisms of attentional biases towards threat in anxiety disorders: an integrative review. *Clin Psychol Rev*. 2010;30(2):203–216.
61. Andero R, Ressler KJ. Fear extinction and BDNF: translating animal models of PTSD to the clinic. *Genes Brain Behav*. 2012;11(5):503–512.
62. Leckman JF, Denys D, Simpson HB, et al. Obsessive-compulsive disorder: a review of the diagnostic criteria and possible subtypes and dimensional specifiers for *DSM-V*. *Depress Anxiety*. 2010;27(6):507–527.
63. Abramowitz JS, Franklin ME, Street GP, et al. Effects of comorbid depression on response to treatment for obsessive-compulsive disorder. *Behav Ther*. 2000;31(3):517–528.
64. Bloch MH. Meta-analysis and moderator analysis: can the field develop further? *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):135–137.
65. Byrne SP, Rapee RM, Richardson R, et al. D-cycloserine enhances generalization of fear extinction in children. *Depress Anxiety*. 2015;32(6):408–414.
66. Hofmann SG, Carpenter JK, Otto MW, et al. Dose timing of D-cycloserine to augment cognitive behavioral therapy for social anxiety: study design and rationale. *Contemp Clin Trials*. 2015;43:223–230.
67. Tuerk PW. Starting from something: augmenting exposure therapy and methods of inquiry. *Am J Psychiatry*. 2014;171(10):1034–1037.