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ORIGINAL ARTICLE

D-Cycloserine-Augmented Behavior Therapy for Body Dysmorphic Disorder: A Preliminary Efficacy Trial

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Abstract
Cognitive behavioral therapy (CBT) is the leading psychotherapeutic treatment for body dysmorphic disorder (BDD), yet not all patients improve. To address the treatment response gap, CBT may be augmented with cognitive enhancers such as D-cycloserine (DCS). DCS-augmented behavior therapy has been tested with mixed results in related disorders. To initially test whether DCS may augment CBT for BDD, we conducted the first preliminary efficacy trial of DCS versus placebo-augmented CBT for BDD, via a randomized, double-blind study. We analyzed data using mixed-effects models in a modified intent-to-treat sample ($N=26$). Over 10 weeks of treatment, primary (BDD severity) and secondary (insight, depression) outcomes improved significantly across both conditions, but there were no significant group differences in response. Exploratory analysis revealed that BDD-related distress, specifically, reduced significantly more in the DCS condition compared to placebo. This is the first study testing DCS-augmented CBT for BDD. Implications, limitations, and future directions are discussed.
Trial registry: ClinicalTrials.gov Identifier NCT00842309

Keywords Body dysmorphic disorder · Behavior therapy · D-Cycloserine · Cognitive enhancers

Introduction

Body dysmorphic disorder (BDD) is a common and severe psychiatric illness, with lifetime prevalence rates ranging from 1.7 to 2.9% (Buhlmann et al. 2010; Koran et al. 2008; Rief et al. 2006; Schieber et al. 2015). BDD involves an excessive preoccupation with one or more imagined or exaggerated flaws in one's physical appearance (American Psychiatric Association [APA] 2013). Appearance preoccupations are accompanied by time-consuming rituals performed to conceal, fix, or reduce distress related to appearance concerns (APA 2013). Reflecting its core features of obsessions and compulsions, BDD is classified as an obsessive compulsive related disorder in the Diagnostic and Statistical Manual-Fifth Edition (DSM-5) (APA 2013). BDD also shares key similarities with social anxiety disorder (SAD), as both illnesses involve a fear of negative evaluation by others (Fang and Hofmann 2010).

Cognitive behavioral therapy (CBT) is a leading empirically-supported treatment for BDD (Veale et al. 2014; Wilhelm et al. 2014). CBT for BDD typically ranges from 12 to 22 sessions and involves psychoeducation, cognitive restructuring, mindfulness, attentional retraining, and a primary emphasis on exposure with ritual prevention (Veale and Neziroglu 2010; Wilhelm et al. 2013). While effective for most BDD patients, not all patients improve with CBT for BDD, and a substantial proportion are left with significant residual symptoms (Veale et al.

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2014; Wilhelm et al. 2014). This gap in treatment response underscores the utility of investigating ways to augment CBT for BDD.

One potential method of augmenting CBT is with a pharmacologic agent that may enhance extinction learning, such as D-cycloserine (DCS). DCS is a partial *N*-methyl-D-aspartic acid (NMDA) receptor agonist which acts on the glutamate system (Davis and Myers 2002). It has been proposed that DCS may enhance fear-based extinction learning in the context of exposure therapy (Mataix-Cols et al. 2017). The effects of DCS on fear-based extinction learning were first demonstrated in animal studies; enhanced extinction learning was observed among rats that were given DCS with extinction training compared to rats that were not given DCS with extinction training (Walker et al. 2002).

In light of promising results in animal models, researchers have examined the benefits of using DCS to augment anxiety or fear extinction in exposure therapy for both SAD (Guastella et al. 2008; Hofmann et al. 2006, 2013) and OCD (Andersson et al. 2015; de Leeuw et al. 2017; Farrell et al. 2013; Kushner et al. 2007; Mataix-Cols et al. 2014; Storch et al. 2007, 2010, 2016; Wilhelm et al. 2008). Whereas results from individual trials were mixed, a large meta-analysis of DCS-augmented behavior therapy shows that overall, DCS significantly augments BT in SAD, but not OCD, trials (Mataix-Cols et al. 2017). Moreover, whereas some individual studies documented a faster response to behavior therapy augmented by DCS compared to placebo (e.g., Hofmann et al. 2013; Chasson et al. 2010), meta-analysis results did not find an advantage of DCS over placebo at mid-treatment (Mataix-Cols et al. 2017).

In light of the mixed findings in related disorders, preliminary efficacy research in BDD is needed to begin to determine whether DCS may be useful in augmenting CBT for BDD. To this end, the present study was the first test of DCS-augmented behavior therapy for BDD. In a randomized, double-blind, controlled trial, we aimed to compare the preliminary efficacy of DCS- versus placebo-augmentation on primary (BDD symptom severity) and secondary (BDD-related insight, depression severity) outcomes over 10 sessions of CBT in adults with BDD ($N = 26$). We also aimed to examine whether those receiving DCS would respond to CBT more quickly, reflected by a greater number of responders at mid-treatment (week 6) among participants in the DCS condition compared to those in the placebo condition. Lastly, given that DCS is hypothesized to enhance fear (or distress)-based extinction learning, specifically, we explored the possibility that DCS-augmentation might specifically impact BDD-related distress, examined separately from other BDD symptoms (e.g., obsessions, rituals), at mid-treatment, post-treatment, and follow-up.

Methods

Participants

Participants included in modified intent-to-treat (ITT) analyses were 26 adults with a primary DSM-IV diagnosis of BDD, who were randomly assigned to receive either CBT plus DCS ($n = 12$) or CBT plus placebo ($n = 14$), and who completed at least one treatment session in their randomized condition (i.e., session 3). See Fig. 1 for a CONSORT diagram depicting participant enrollment and study flow. To be eligible, participants had to be at least 18 years old and score ≥ 24 on the Yale-Brown Obsessive Compulsive Scale Modified for BDD (BDD-YBOCS) (Phillips et al. 1997). Participants were excluded if they were pregnant or breastfeeding, were taking medications that could interfere with DCS or lower the seizure threshold (e.g., clozapine; pethidine), tested positive for non-prescribed drugs of abuse, had a history of seizures or other serious medical illnesses, or had comorbid alcohol dependence, psychosis, bipolar disorder, borderline personality disorder, developmental disorder, or an organic mental disorder. Participants were also excluded if they had current active suicidal or homicidal intent, were in current psychotherapy, or had not benefited from ten or more prior CBT sessions. Participants taking psychotropic medications were required to be on a stable dose for at least 2 months before enrolling in the study, and medications were required to remain stable throughout study treatment and follow-up. Baseline demographic characteristics are described in Table 1, and comorbid secondary psychiatric diagnoses and medication status are reported in Table 2.

Procedures

Participants were recruited through the Massachusetts General Hospital Obsessive Compulsive Disorder (OCD) and Related Disorders Program and learned about the opportunity to participate through calling the program's research or clinic phone lines. Following a full explanation of study procedures, written informed consent was obtained from all participants. Study clinicians trained in assessing and providing CBT for BDD conducted all assessments and treatment. Study clinicians included licensed psychologists, postdoctoral fellows in clinical psychology, pre-doctoral clinical psychology interns, and Masters-level clinical psychology doctoral students. Study clinicians met weekly for supervision with a licensed psychologist specializing in CBT for BDD. All study procedures were approved by the Massachusetts General Hospital institutional review board.

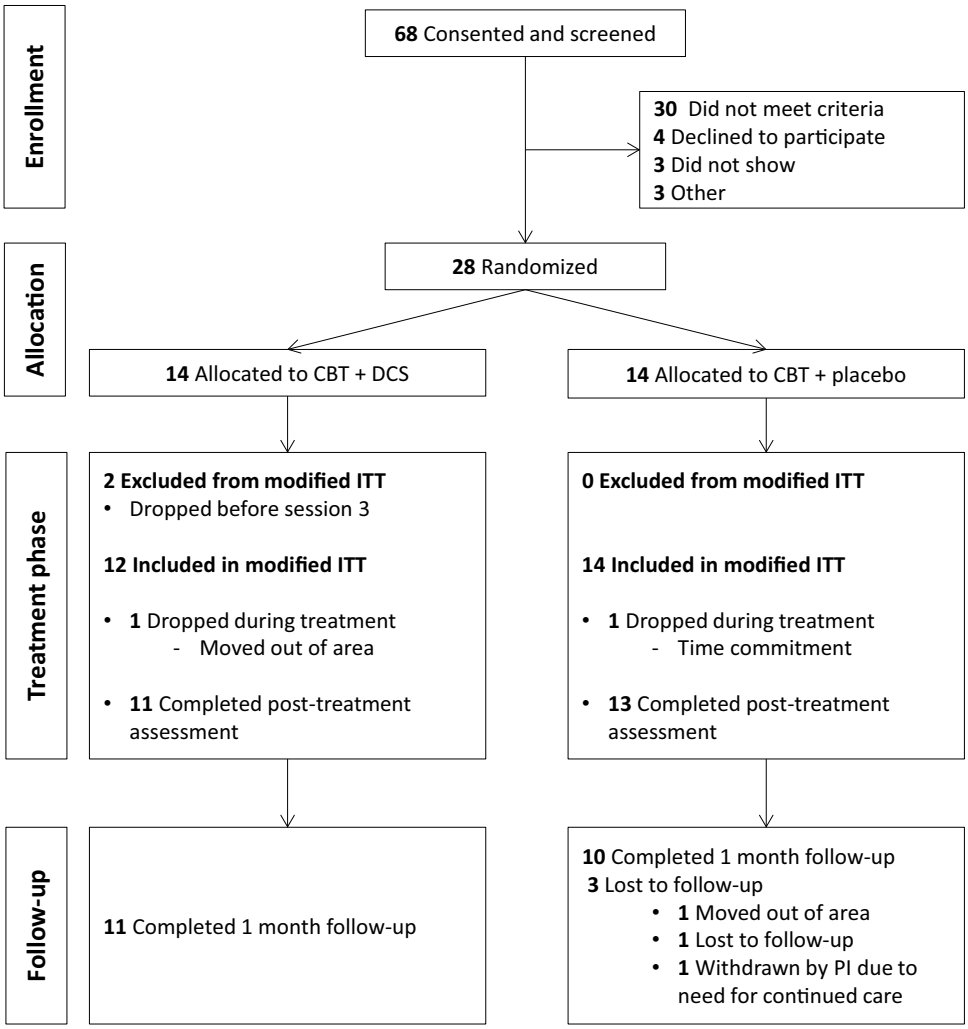

Fig. 1 CONSORT diagram of participant flow. *CBT + DCS* cognitive behavioral therapy augmented with D-cycloserine, *CBT + placebo* cognitive behavioral therapy augmented with placebo, *ITT* intent-to-treat

Assessments

To establish eligibility, participants completed an initial diagnostic screening assessment with the trained study clinician, which also included a urine drug screen to test for opiates, phencyclidine, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamine, and marijuana, a pregnancy test for females, and a medical screening by a study physician to evaluate whether use of DCS was medically appropriate. Following the initial screening visit, assessments were administered weekly (BDD severity, depression) or every 2 weeks (BDD-related insight) at therapy sessions, post-treatment, and 1-month follow-up by the study clinician. Participants also completed self-report measures, including an assessment of depression severity.

Cognitive Behavioral Therapy

Following the screening assessment, eligible participants completed a 90-min pre-treatment psychoeducation and treatment planning visit. The study clinician explained the cognitive behavioral model of BDD, helped the participant to develop an individualized cognitive behavioral model of his or her BDD symptoms, and explained the treatment approach and rationale. The therapist and participant also developed an exposure hierarchy. Subsequently, participants completed 10 weekly 60-min CBT sessions. Sessions 1 and 2 focused on cognitive interventions—no DCS or placebo pills were administered prior to these sessions. Sessions 3 through 10 focused on exposure with ritual prevention, including incorporation of mirror retraining work, preceded by study medication.

Medication Augmentation

The research pharmacy at Massachusetts General Hospital maintained the double-blind design, by assigning participants to a treatment condition (CBT augmented with either 100 mg DCS or placebo) and dispensing study medications. Participants were randomly allocated to a condition at a

Table 1 Baseline demographic characteristics of the sample by treatment assignment

	D-Cycloserine ($n=12$) M (SD)	Placebo ($n=14$) M (SD)	X^2/t	p-value
Age	23.92 (5.74)	29.07 (11.04)	1.41	0.17
Age of BDD onset	14.83 (3.69)	19.21 (12.57)	1.12	0.27
	n (%)	n (%)		
Race			0.05[a]	0.99
American Indian/Alaska native	1 (8.3)	–		
White	11 (91.7)	11 (78.6)		
Black or African American	–	1 (7.1)		
More than one race	–	1 (7.1)		
Unknown or not reported	–	1 (7.1)		
Ethnicity			0.02[a]	0.89
Hispanic or Latino	1 (8.3)	2 (14.3)		
Sex			3.76[a]	0.052
Female	5 (41.6)	12 (85.7)		
Marital status			0.05[a]	0.98
Divorced	1 (8.3)	–		
Married	2 (16.7)	3 (21.4)		
Single	9 (75.0)	11 (78.6)		
Employment			1.62[a]	0.81
Working full-time	3 (25.0)	4 (28.6)		
Working part-time	2 (16.7)	3 (21.4)		
Student	4 (33.3)	1 (7.1)		
Unemployed	3 (25.0)	4 (28.6)		
Other	–	2 (14.3)		
Education			0.29[a]	0.96
College	3 (25.0)	6 (42.9)		
High school	4 (33.3)	5 (35.7)		
Other	2 (16.7)	1 (7.1)		
Post-graduate	3 (25.0)	2 (14.3)		

[a]Yates Chi square correction for continuity used for cell values < 5

50/50 ratio, without stratifying by demographic or clinical characteristics. The research coordinator administered the study medication to participants 1 h before each exposure session (sessions 3–10). Participants were instructed to refrain from consuming alcohol 12 h prior to and 24 h after receiving the study medication. Immediately before administering the study medication to participants, the research coordinator administered a saliva test to confirm the absence of alcohol in saliva.

Measures

Diagnostic Assessment

The Structured Clinical Interview for DSM-IV (SCID-I-RV) (First et al. 2002) was administered by the clinician at the screening visit, to evaluate diagnostic eligibility criteria. The SCID-I-RV is the gold-standard, semi-structured clinician-administered diagnostic assessment for major DSM-IV psychiatric illnesses. (First et al. 2002).

Primary Outcome

The Yale-Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS) (Phillips et al. 1997), a gold-standard clinician-administered assessment of past-week BDD severity, was the primary outcome measure. The BDD-YBOCS is semi-structured and has strong psychometric properties including test–retest and inter-rater reliability, sensitivity to change, and internal consistency (Phillips et al. 2014). In the present sample, internal consistency at baseline was adequate (Cronbach's alpha = 0.68). The BDD-YBOCS has 12 items, with total scores that range from 0 to 48; higher scores reflect greater BDD symptom severity.

Table 2 Clinical characteristics of the sample at baseline by treatment assignment

	D-Cycloserine ($n=12$) n (%)	Placebo ($n=14$) n (%)	X^2	p-value
At least 1 comorbid diagnosis	8 (66.7)	10 (71.4)	0.027	0.87
Common comorbidities[a]				
Major depressive disorder	4 (33.3)	3 (21.4)	0.06[b]	0.81
Dysthymia	2 (16.7)	1 (7.1)	0.02[b]	0.89
Obsessive compulsive disorder	1 (8.3)	3 (21.4)	0.14[b]	0.71
Medication				
Taking psychotropics at baseline[c]	3 (25.0)	9 (64.3)	2.59[b]	0.11
Stimulants	–	2 (14.3)	0.39[b]	0.53
Benzodiazepines	1 (8.3)	2 (14.3)	0.02[b]	0.89
SSRIs	3 (25.0)	8 (57.1)	1.58[b]	0.21

SSRIs selective serotonin reuptake inhibitors

[a]Only lists disorders which have > 10% prevalence in either treatment arm. Additionally, the following DSM-IV comorbid diagnoses were also present in the sample (< 10%): social anxiety disorder, specific phobia, posttraumatic stress disorder, generalized anxiety disorder, chronic tic disorder, panic disorder, bulimia nervosa, binge eating disorder

[b]Yates Chi square correction for continuity used for cell values < 5

[c]Some subjects reported more than one class of medication at baseline

Secondary Outcomes

We measured BDD-related insight with the gold-standard Brown Assessment of Beliefs Scale (BABS) (Eisen et al. 1998). The BABS is a seven-item clinician-administered semi-structured interview. Scores range from 0 to 24, with higher scores corresponding with poorer insight (i.e., belief that one's appearance concerns are due to a true physical defect, as opposed to BDD). A total score of ≥ 18 plus a 4 on the item measuring conviction indicates delusionality. The BABS has strong inter-rater reliability, test–retest reliability, internal consistency, and construct validity (Phillips et al. 2013). In the present study, internal consistency was strong at baseline (Cronbach's alpha = 0.82).

We measured depression severity with the self-report Beck Depression Inventory-II (Beck et al. 1996). The total score, calculated by summing the 21 items, ranges from 0 to 63. Higher scores indicate more severe depression symptoms, with scores ≥ 20 indicating moderate to severe depression. The BDI-II is widely-used and well-validated, and in the present study it demonstrated strong internal consistency at baseline (Cronbach's alpha = 0.94).

Exploratory Outcome

Distress associated with BDD-related thoughts or actions was measured with the BDD-YBOCS items 3 ("Distress associated with thoughts about body-defect") and 8 ("Distress associated with activities related to body defect"), which were each rated on 5-point Likert scales ranging from 0, indicating no distress, to 4, indicating extreme distress. The two items were averaged for analysis.

Statistical Analyses

We used SAS software Version 9.4 to conduct analyses (SAS Institute, 2016). We first visually inspected variables for normality. Using *t*-tests for continuous variables and Chi square tests for categorical variables, we examined group differences in baseline demographic and clinical characteristics, and we examined differences among participants who did or did not complete the 1-month follow-up assessment. Primary modified ITT analyses included all participants who attended at least one post-randomization exposure therapy visit (i.e., session 3 onward) in their assigned treatment condition. We followed up modified ITT analyses using last observation carried forward, which yielded the same pattern of results and are therefore not presented. If participants had < 20% items missing on a given scale, scale scores were calculated using person-mean imputation; this affected 1.2%, 0%, and 3.3% of the available BDD-YBOCS, BABS, and BDI-II scales, respectively. Hedges' *g* (1981) was used as the measure of all effect sizes. Hedge's *g* uses the pooled standard deviation weighted for sample size, to account for different sample sizes between groups (Hedges and Olkin 1985). As this was a pilot study with a small sample, no adjustments were made for multiple comparisons.

Group Differences in Treatment Response

To examine group differences in treatment response, we conducted three mixed-model repeated-measures analyses for the three dependent variables, respectively: (1) BDD severity (BDD-YBOCS), (2) BDD-related insight (BABS), and (3) depression severity (BDI-II) (Gueorguieva and Krystal 2004). Condition (DCS, placebo), time (screening, treatment planning, therapy sessions [sessions 1–10 for BDD Y-BOCS and BDI-II; sessions 2, 4, 6, 8, 10 for BABS], post-treatment, 1-month follow-up), and condition-by-time interaction terms were included as fixed effects, and repeated measures of participants were modeled with a heterogeneous Toeplitz covariance structure. Of note, all available time points for each outcome (i.e., up to 14 for BDD-YBOCS and BDI-II, up to 9 for BABS) were included in mixed models, to increase power. Overall therapy effect (not treatment-specific) was evaluated with a specific contrast of linear change in symptom severity estimates from screening through post-treatment. To evaluate whether symptom changes varied by treatment condition, we used specific contrasts to evaluate whether linear change slopes in symptom severity from week 2 (last visit before DCS-augmentation) to post-treatment or 1-month follow-up differed between treatment conditions. We also report simple treatment differences at mid-treatment (week 6), post-treatment, and 1-month follow-up for each outcome.

To parallel our primary mixed-effect analyses, we also examined differences in responder status by condition at post-treatment and 1-month follow up, using Chi-squares. Responder status was defined as a $\geq 30\%$ reduction in BDD-YBOCS score (Phillips et al. 2014).

Early Response

To examine whether those in DCS-augmented CBT met treatment responder status earlier than those in placebo-augmented CBT, we examined differences in responder status at week 6 (mid-exposure treatment) using Chi square.

Treatment Effect on Subjective Distress

Finally, to examine whether participants in the DCS-augmented CBT treatment reported greater changes in distress associated with BDD-related thoughts or actions compared to those in placebo-augmented CBT, we used repeated measures mixed models analogous to the model described for the total BDD-YBOCS scores, using the average of BDD-YBOCS items 3 and 8 as the outcome.

Results

Preliminary Results

No serious adverse events were reported in either condition. Variables appeared normally distributed. No significant differences were observed in demographic characteristics, comorbidity, or medication status between groups at baseline (see Tables 1, 2). No significant differences were observed at baseline in demographic or clinical characteristics between those who did versus did not complete the 1-month follow-up assessment ($ps > .05$).

Overall Therapy Effects

There was a significant overall effect of time (screening to post-treatment) for each of the three outcome measures. Specifically, BDD severity [estimated mean change [95% CI]; −9.90 [−11.52, −8.28], t (df = 49.1) = −12.27; $p < 0.001$], insight [−5.12 [−6.34, −3.90], t (df = 43.1) = −8.48; $p < 0.001$], and depression [−5.04 [−7.12, −2.96], t (df = 33.4) = −4.93; $p < 0.001$] each improved significantly with large effects across 10 weeks of treatment (Table 3).

Group Differences in Treatment Response

To test our primary hypotheses, we examined treatment differences in the linear change slopes in clinical outcomes from week 2 (the last session before DCS augmentation) to post-treatment and 1-month follow-up. We were unable to detect any statistically significant treatment differences in BDD symptom severity (Fig. 2), insight, or depression severity up until either post-treatment (estimated slope difference [95%CI]; BDD-YBOCS: −1.41 [−5.12, 2.30], t (df = 38.7) = −0.77, $p = 0.447$; BABS: −1.24 [−3.88, 1.40], t (df = 41.0) = −0.95, $p = 0.349$; BDI-II: −1.74 [−5.97, 2.50], t (df = 40.3) = −0.83, $p = 0.412$) or 1-month follow-up (estimated slope difference [95%CI]; BDD-YBOCS: −1.90 [−5.84, 2.05], t (df = 36.2) = −0.98, $p = 0.336$; BABS: 0.07 [−2.91, 3.04], t (df = 26.1) = 0.05, $p = 0.964$; BDI-II: −2.29 [−6.44, 1.86], t (df = 38.1) = −1.12, $p = 0.271$). Indeed, a visual inspection of BDD-YBOCS scores by treatment condition (Fig. 2) and a comparison of group means at various time points throughout the treatment period (Table 3) demonstrates that the two groups' responses closely tracked one another throughout the treatment.

To parallel the mixed model test of our primary outcome, we also examined group differences in responder status at post-treatment and 1-month follow-up. Chi square analyses revealed no group differences in responder status at post-treatment (Yates correction $X^2 = 0.10$, $p = 0.75$) or

Table 3 Baseline, mid-treatment, and post-treatment scores

Outcome	Placebo Mean (SD)	Active Mean (SD)	Between group effect size [95% CI][a]	Between group statistics[b]
BDD-YBOCS				
Screening	30.36 (4.45)	31.75 (5.03)	0.28 [−0.49, 1.06]	$F(1, 19.5) = 0.35$, $p = 0.56$
Week 2[c]	27.64 (6.81)	30.08 (4.89)	0.39 [−0.39, 1.17]	$F(1, 27.4) = 1.17$, $p = 0.29$
Mid-treatment	20.85 (8.91)	21.75 (5.34)	0.12 [−0.67, 0.90]	$F(1, 27.6) = 0.33$, $p = 0.57$
Post-treatment	18.77 (10.03)	19.64 (6.80)	0.10 [−0.71, 0.90]	$F(1, 25.4) = 0.06$, $p = 0.80$
1-month follow-up	17.70 (9.17)	19.45 (6.25)	0.22 [−0.64, 1.08]	$F(1, 23.6) < 0.01$, $p = 0.98$
Within-tx effect size week 0 to post-tx[a,d]	−1.47 [−2.32, −0.62]	−1.97 [−2.96, −0.97]		
Within-tx effect size week 2 to post-tx[a,d]	−1.01 [−1.81, −0.21]	−1.71 [−2.67, −0.76]		
BABS				
Screening	13.14 (5.64)	13.92 (3.63)	0.16 [−0.62, 0.93]	$F(1, 22.5) = 0.13$, $p = 0.73$
Week 2[c]	12.00 (5.94)	13.42 (4.98)	0.25 [−0.52, 1.02]	$F(1, 24.0) = 0.43$, $p = 0.52$
Mid-treatment	9.69 (5.06)	9.42 (3.80)	−0.06 [−0.84, 0.73]	$F(1, 25.9) < 0.01$, $p = 0.99$
Post-treatment	8.69 (6.98)	7.91 (4.21)	−0.13 [−0.93, 0.68]	$F(1, 23.7) = 0.02$, $p = 0.88$
1-month follow-up	7.70 (5.83)	10.0 (5.39)	0.39 [−0.47, 1.26]	$F(1, 18.7) = 0.77$, $p = 0.39$
Within-tx effect size week 0 to post-tx[a,d]	−0.68 [−1.46, 0.09]	−1.48 [−2.40, −0.56]		
Within-tx effect size week 2 to post-tx[a,d]	−0.50 [−1.26, 0.27]	−1.15 [−2.03, −0.26]		
BDI-II				
Screening	20.08 (13.14)	22.55 (13.92)	0.18 [−0.63, 0.98]	$F(1, 21.7) = 0.04$, $p = 0.84$
Week 2[c]	15.58 (12.08)	17.33 (11.75)	0.14 [−0.64, 0.93]	$F(1, 22.7) = 0.12$, $p = 0.73$
Mid-treatment	15.42 (12.77)	13.37 (11.22)	−0.16 [−0.97, 0.64]	$F(1, 24.2) = 0.04$, $p = 0.84$
Post-treatment	15.70 (12.75)	11.27 (11.65)	−0.35 [−1.17, 0.48]	$F(1, 23.3) = 0.43$, $p = 0.52$
1-month follow-up	11.15 (12.48)	11.45 (10.47)	0.03 [−0.89, 0.94]	$F(1, 21.5) = 0.31$, $p = 0.58$
Within-tx effect size week 0 to post-tx[a,d]	−0.33 [−1.12, 0.46]	−0.85 [−1.72, 0.03]		
Within-tx effect size week 2 to post-tx[a,d]	0.01 [−0.78, 0.79]	−0.50 [−1.33, 0.33]		
BDD-YBOCS distress items				
Screening	2.43 (0.55)	2.92 (0.36)	1.00 [0.19, 1.82]	$F(1, 22.5) = 5.08$, $p = 0.03$
Week 2[c]	2.32 (0.75)	2.79 (0.54)	0.69 [−0.11, 1.48]	$F(1, 27.0) = 3.31$, $p = 0.08$
Mid tx	1.81 (0.75)	2.13 (0.68)	0.43 [−0.36, 1.23]	$F(1, 26.2) = 2.16$, $p = 0.15$
Post tx	1.73 (0.86)	1.82 (0.68)	0.11 [−0.69, 0.91]	$F(1, 26.2) = 0.15$, $p = 0.70$
1-month follow-up	1.70 (1.06)	1.82 (0.68)	0.13 [−0.73, 0.99]	$F(1, 22.0) = 0.06$, $p = 0.81$
Within-tx effect size week 0 to post-tx[a,d]	−0.95 [−1.74, −0.15]	−1.98 [−2.97, −0.98]		
Within-tx effect size week 2 to post-tx[a,d]	−0.71 [−1.49, 0.07]	−1.53 [−2.46, −0.60]		

BDD-YBOCS Yale-Brown Obsessive Compulsive Scale Modified for BDD, *BABS* Brown Assessment of Beliefs Scale, *BDI-II* Beck Depression Inventory-II, *tx* treatment

[a]Effect sizes were calculated as Hedge's *g* [95% CI]

[b]*F*-tests and *p*-values reported are based on model-based post-hoc group differences at each time-point indicated

[c]DCS-augmentation started at week 3; week 2 is the last week without DCS augmentation

[d]Both the overall effect of treatment from screening to the end-of-treatment and the effect size from the start of DCS-augmentation (after week 2) to the end-of-treatment are presented to enable the comparison of overall treatment effects and treatment effects partially due to DCS-augmentation

1-month follow-up (Yates correction $X^2 = 0.02$, $p = 0.90$). Seven (58.33%) participants in the DCS condition and eight (66.7%) participants in the placebo condition were treatment responders at post-treatment.

Early Response

Chi square analysis revealed no group differences in responder status at mid-treatment (Yates correction

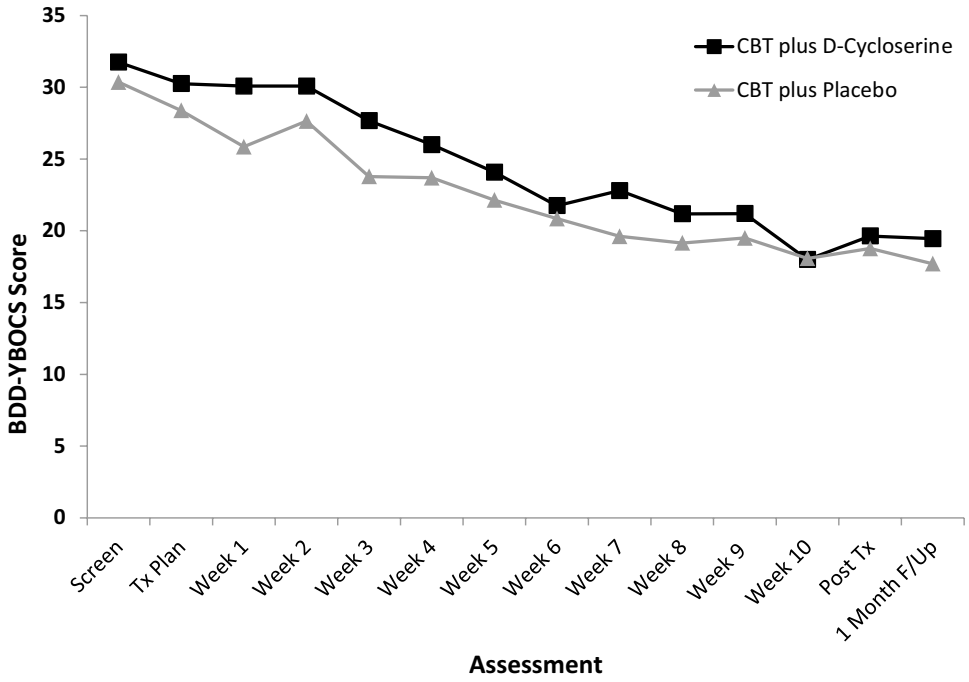

Fig. 2 BDD Y-BOCS scores by treatment condition from baseline through 1-month follow-up. *BDD-YBOCS* Yale-Brown Obsessive Compulsive Scale Modified for BDD, *Tx* treatment, *F/Up* follow-up

$X^2 = 0.04$, $p = 0.84$), suggesting that DCS-augmentation did not yield early treatment response compared to placebo-augmented CBT for BDD. Examination of effect sizes and differences in symptom scores likewise indicated that no clinically meaningful differences emerged in BDD severity between groups at mid-treatment (see Table 3). Moreover, visual inspection of BDD-YBOCS scores by condition over time suggest that both treatment conditions responded to CBT at a similar rate (see Fig. 2).

Treatment Effect on Subjective Distress

Subjective distress associated with BDD-related thoughts and activities decreased throughout the treatment period, and the changes in distress associated with BDD-related activities differed by treatment condition. Compared to participants in the placebo treatment, participants in the DCS-augmentation arm experienced greater decreases in distress associated with BDD-related thoughts and activities from week 2 (the last week before DCS augmentation) to post-treatment (estimated slope difference [95%CI]: −0.36 [−0.71, −0.004], t (df = 35.4) = −2.05, $p = 0.047$) and to follow-up (−0.42 [−0.83, −0.01], t (df = 31.3) = −2.11, $p = 0.043$). From week 2 to mid-treatment (week 6), we were not able to detect any difference in the treatment change slopes (−0.17 [−0.51, 0.17], t (df = 79.7) = −1.00, $p = 0.319$).

Discussion

To the best of our knowledge, this study is the first to test whether DCS augments response to CBT for BDD. In light of mixed results in DCS-augmentation trials for related disorders (Mataix-Cols et al. 2017), it is difficult to draw inferences from the extant literature. Therefore, we aimed to conduct the first preliminary efficacy trial in BDD. Using a randomized, double-blind, placebo-controlled design, results preliminarily suggest that overall, DCS does not enhance BDD treatment effectiveness above placebo. This result was consistent when examining BDD severity, BDD-related insight, and depression severity as outcomes, and when we followed up mixed-effects analyses with examination of group differences in responder status at post-treatment and 1-month follow-up. Moreover, this study extends that evidence to a novel clinical use case. Very small between-group effects at mid-point and examination of BDD-YBOCS scores by condition over time also suggest that DCS did not yield early response to CBT for BDD, compared to placebo. This finding is consistent with meta-analysis results from DCS trials conducted in anxiety disorders and OCD (Mataix-Cols et al. 2017).

It is possible that null primary and secondary results in the present trial are attributable to the outcomes examined. DCS is a cognitive enhancer hypothesized to augment

fear-based extinction learning. To this end, most prior trials have examined DCS augmentation of behavior therapy for anxiety-related outcomes. It is possible that extinction learning mechanisms are less relevant when overall BDD severity, depression, and BDD-related insight are the treatment targets. Consistent with this hypothesis, it is notable that the only significant finding in the present study emerged with regard to our exploratory analysis examining the effect of DCS- versus placebo-augmented CBT on BDD-related distress, specifically. Results showed that BDD-related distress reduced significantly more in the DCS arm, compared to the placebo arm. Future trials that seek to extend DCS research in BDD should further examine distress or anxiety-based outcomes as a primary target.

In light of the mixed findings across DCS augmentation trials, researchers have more recently begun to consider potential moderators of the effect of DCS on response to behavior therapy (Otto et al. 2016; Hofmann et al. 2015; Hofmann 2016). Andersson and colleagues (2015) found that SSRI medication status moderated the effect of DCS on response to behavior therapy, such that those taking SSRI medications demonstrated an impaired response to treatment in the DCS (but not placebo) condition compared to those who were not taking SSRI medications (Andersson et al. 2015). As a result, a recent editorial called for examination of SSRI use as a moderator in DCS trials (Hofmann 2016). On the other hand, meta-analysis results did not find a significant moderation effect for SSRI status across trials (Mataix-Cols et al. 2017). Relatedly, researchers have tested whether the success of exposure exercises moderates the effect of DCS on response to behavior therapy. In other words, DCS may enhance learning for both "successful" and "unsuccessful" exposure exercises, such that the overall benefits of DCS may wash out over time if given indiscriminately before each session (Hofmann 2016). One prior study of DCS-augmented behavior therapy for SAD supports this hypothesis, showing that DCS may be beneficial specifically when paired only with "successful," but not "unsuccessful," exposure sessions (Smits et al. 2013). In the present study, power limitations prohibited us from testing these potential moderation effects; however, moderation hypotheses merit examination in future research.

The present study had several important strengths, including use of a randomized, double-blind, and placebo-controlled design, a sample diagnosed using gold-standard clinician-administered assessments, and first examination of DCS in a novel diagnostic group. Moreover, given the limited literature on BDD treatment more broadly, this study is among the first published randomized clinical trials of CBT for BDD in general. Given the preliminary nature of this study, results should also be interpreted in light of limitations. As an initial efficacy trial, the sample size was small and we were underpowered. Thus, effect sizes may not be reliable (e.g., they likely have large confidence intervals). Use of mixed models that included up to 14 time points per outcome increased power to detect effects. However, to draw firm conclusions about the efficacy of DCS-augmented behavior therapy for BDD, a larger trial would be needed. A larger sample would also enable a more nuanced examination of moderators, as emphasized by Hofmann (2016). Second, the same individuals served as clinicians and assessors. All clinician-assessors and patients were blind to patients' study condition (i.e., DCS, placebo). Thus, it is unlikely that using the same study staff as both clinicians and blind assessors influenced group differences in response to treatment. On the other hand, it is possible that clinicians' investment in the success of their therapy may have influenced overall assessment of response to treatment, across both conditions. Thus, we should infer overall effect sizes for response to CBT for BDD from studies that used randomization with independent evaluators (e.g., Veale et al. 2014; Wilhelm et al. 2014).

Altogether, there is mounting mixed evidence regarding DCS-augmented CBT across psychiatric disorders. It is possible that DCS is not a useful method of augmenting the speed or efficacy of behavior therapy. It is also possible that DCS may only be effective in specific circumstances, such as when given in the absence of SSRI medication (Andersson et al. 2015; Hofmann 2016), or when administered only after "effective" exposure exercises (Hofmann et al. 2015; Hofmann 2016; Smits et al. 2013). Moreover, it is possible that DCS augmentation may be most useful in cases where patients have difficulty consolidating learning. In this case, DCS augmentation could be reserved for times when habituation to standalone behavior therapy is not generalizing sufficiently across sessions. As a next step building from this research, it is important to consider alternative fruitful avenues for enhancing treatment effectiveness in BDD. For example, precision medicine efforts aimed at identifying which treatments work best for whom may offer promise in terms of enhancing treatment effectiveness for BDD in the future.

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Compliance with Ethical Standards

Conflict of interest Drs. Weingarden and Wilhelm and Ms. Ladis have received salary support from Telefonica Alpha, Inc. Dr. Wilhelm has received research support in the form of free medication and matching

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Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Animal Rights No animal studies were carried out by the authors for this article.

References

American Psychiatric Association [APA]. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Association.

Andersson, E., Hedman, E., Enander, J., Djurfeldt, D. R., Ljótsson, B., Cervenka, S., Isung, J., Svanborg, C., Mataix-Cols, D., Kaldo, V., Andersson, G., Lindefors, N., & Rück, C. (2015). D-Cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: A randomized clinical trial. *JAMA Psychiatry, 72*, 659–667. https://doi.org/10.1001/jamapsychiatry.2015.0546.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Beck depression inventory-second edition: manual*. San Antonio, TX: Psychological Corporation.

Buhlmann, U., Glaesmer, H., Mewes, R., Fama, J. M., Wilhelm, S., Brähler, E., & Rief, W. (2010). Updates on the prevalence of body dysmorphic disorder: A population-based survey. *Psychiatry Research, 178*, 171–175. https://doi.org/10.1016/j.psychres.2009.05.002.

Chasson, G. S., Buhlmann, U., Tolin, D. F., Rao, S. R., Reese, H. E., Rowley, T., Welsh, K., & Wilhelm, S. (2010). Need for speed: Evaluating slopes of OCD recovery in behavior therapy enhanced with D-cycloserine. *Behaviour Research and Therapy, 48*, 675–679. https://doi.org/10.1016/j.brat.2010.03.007.

Davis, M., & Myers, K. M. (2002). The role of glutamate and gamma-aminobutyric acid in fear extinction: Clinical implications for exposure therapy. *Biological Psychiatry, 52*, 998–1007.

de Leeuw, A. S., van Megen, H. J. G. M., Kahn, R. S., & Westenberg, H. G. M. (2017). D-Cycloserine addition to exposure sessions in the treatment of patients with obsessive-compulsive disorder. *European Psychiatry, 40*, 38–44. https://doi.org/10.1016/j.eurpsy.2016.06.011.

Eisen, J. L., Phillips, K. A., Baer, L., Beer, D. A., Atala, K. D., & Rasmussen, S. A. (1998). The Brown Assessment of Beliefs Scale: Reliability and validity. *American Journal of Psychiatry. 155*. 102–108. https://doi.org/10.1176/ajp.155.1.102..

Fang, A., & Hofmann, S. G. (2010). Relationship between social anxiety disorder and body dysmorphic disorder. *Clinical Psychology Review, 30*, 1040–1048. https://doi.org/10.1016/j.cpr.2010.08.001.

Farrell, L. J., Waters, A. M., Boschen, M. J., Hattingh, L., McConnell, H., Milliner, E. L., Collings, N., Zimmer-Gembeck, M., Shelton, D., Ollendick, T. H., Testa, C., & Storch, E. A. (2013). Difficult-to-treat pediatric obsessive-compulsive disorder: Feasibility and preliminary results of a randomized pilot trial of D-cycloserine-augmented behavior therapy. *Depression and Anxiety, 30*, 723–731. https://doi.org/10.1002/da.22132.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002). *The structured clinical interview for the DSM-IV-TR Axis I disorders (SCID-I/P). (Research version, patient ed.)*. New York: Biometrics Research.

Guastella, A. J., Richardson, R., Lovibond, P. F., Rapee, R. M., Gaston, J. E., Mitchell, P., & Dadds, M. R. (2008). A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. *Biological Psychiatry, 63*, 544–549. https://doi.org/10.1016/j.biopsych.2007.11.011.

Gueorguieva, R., & Krystal, J. H. (2004). Move over ANOVA: Progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Archives of General Psychiatry, 61*, 310–317. https://doi.org/10.1001/archpsyc.61.3.310.

Hedges, L., & Olkin, I. (1985). *Statistical methods for meta-analysis*. New York: Academic Press.

Hedges, L. V. (1981). Distribution theory for Glass's estimator of effect size and related estimators. *Journal of Educational and Behavioral Statistics, 6*, 107–128. https://doi.org/10.3102/10769986006002107.

Hofmann, S. G. (2016). Schrödinger's cat and D-cycloserine to augment exposure therapy-both are alive and dead. *JAMA Psychiatry, 73*, 771–772. https://doi.org/10.1001/jamapsychiatry.2016.1132.

Hofmann, S. G., Carpenter, J. K., Otto, M. W., Rosenfield, D., Smits, J. A. J., & Pollack, M. H. (2015). Dose timing of D-cycloserine to augment cognitive behavioral therapy for social anxiety: Study design and rationale. *Contemporary Clinical Trials, 43*, 223–230. https://doi.org/10.1016/j.cct.2015.06.015.

Hofmann, S. G., Meuret, A. E., Smits, J. A., Simon, N. M., Pollack, M. H., Eisenmenger, K., Shiekh, M., & Otto, M. W. (2006). Augmentation of exposure therapy with D-cycloserine for social anxiety disorder. *Archives of General Psychiatry, 63*, 298. https://doi.org/10.1001/archpsyc.63.3.298.

Hofmann, S. G., Otto, M. W., Pollack, M. H., & Smits, J. A. (2015). D-Cycloserine augmentation of cognitive behavioral therapy for anxiety disorders: An update. *Current Psychiatry Reports, 17*, 532. https://doi.org/10.1007/s11920-014-0532-2.

Hofmann, S. G., Smits, J. A., Rosenfield, D., Simon, N. M., Otto, M. W., Meuret, A. E., Fang, A., Tart, C., & Pollack, M. H. (2013). D-Cycloserine as an augmentation strategy with cognitive-behavioral therapy for social anxiety disorder. *America Journal of Psychiatry, 170*, 751–758. https://doi.org/10.1176/appi.ajp.2013.12070974.

Koran, L. M., Abujaoude, E., Large, M. D., & Serpe, R. T. (2008). The prevalence of body dysmorphic disorder in the United States adult population. *CNS Spectrums, 13*, 316–322.

Kushner, M. G., Kim, S. W., Donahue, C., Thuras, P., Adson, D., Kotlyar, M., McCabe, J., Peterson, J., & Foa, E. B. (2007). D-Cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biological Psychiatry, 62*, 835–838. https://doi.org/10.1016/j.biopsych.2006.12.020.

Mataix-Cols, D., Fernández de la Cruz, L., Monzani, B., Rosenfield, D., Andersson, E., Pérez-Vigil, A., & Rück, C. (2017). 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. *JAMA Psychiatry, 74*, 501–510. https://doi.org/10.1001/jamapsychiatry.2016.3955.

Mataix-Cols, D., Turner, C., Monzani, B., Isomura, K., Murphy, C., Krebs, G., & Heyman, I. (2014). Cognitive-behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive-compulsive disorder: Pilot randomised controlled trial. *British Journal of Psychiatry, 204*, 77–78. https://doi.org/10.1192/bjp.bp.113.126284.

Otto, M. W., Kredlow, M. A., Smits, J. A. J., Hofmann, S. G., Tolin, D. F., de Kleine, R. A., van Minnen, A., Evins, A. E., & Pollack, M. H. (2016). Enhancement of psychosocial treatment with D-cycloserine: Models, moderators, and future directions. *Biological Psychiatry, 80*, 274–283. https://doi.org/10.1016/j.biopsych.2015.09.007.

Phillips, K. A., Hart, A. S., & Menard, W. (2014). Psychometric evaluation of the Yale-Brown Obsessive-Compulsive Scale Modified for Body Dysmorphic Disorder (BDD-YBOCS). *Journal of Obsessive Compulsive and Related Disorders, 3*, 205–208.

Phillips, K. A., Hart, A. S., Menard, W., & Eisen, J. L. (2013). Psychometric evaluation of the Brown Assessment of Beliefs Scale in body dysmorphic disorder. *Journal of Nervous and Mental Disease, 201*, 640–643. https://doi.org/10.1097/NMD.0b013e3182983041.

Phillips, K. A., Hollander, E., Rasmussen, S. A., & Aronowitz, B. R. (1997). A severity rating scale for body dysmorphic disorder: Development, reliability, and validity of a modified version of the Yale-Brown Obsessive Compulsive Scale. *Psychopharmacology Bulletin, 33*, 17–22.

Rief, W., Buhlmann, U., Wilhelm, S., Borkenhagen, A., & Brahler, E. (2006). The prevalence of body dysmorphic disorder: A population-based survey. *Psychological Medicine, 36*, 877–885. https://doi.org/10.1017/S0033291706007264.

SAS Institute, Inc. (2016). *The SAS system for Windows, version 9.4*. Cary, NC: SAS Institute, Inc.

Schieber, K., Kollei, I., de Zwaan, M., & Martin, A. (2015). Classification of body dysmorphic disorder—What is the advantage of the new DSM-5 criteria? *Journal of Psychosomatic Research, 78*, 223–227. https://doi.org/10.1016/j.jpsychores.2015.01.002.

Smits, J. A. J., Rosenfield, D., Otto, M. W., Marques, L., Davis, M. L., Meuret, A. E., Simon, N. M., Pollack, M. H., & Hofmann, S. G. (2013). D-Cycloserine enhancement of exposure therapy for social anxiety disorder depends on the success of exposure sessions. *Journal of Psychiatric Research, 47*, 1455–1461. https://doi.org/10.1016/j.jpsychires.2013.06.020.

Storch, E. A., Merlo, L. J., Bengtson, M., Murphy, T. K., Lewis, M. H., Yang, M. C., Jacob, M. L., Larson, M., Hirch, A., Fernandez, M., Geffken, G. R., & Goodman, W. K. (2007). D-Cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *International Clinical Psychopharmacology, 22*, 230–237. https://doi.org/10.1097/YIC.0b013e32819f8480.

Storch, E. A., Murphy, T. K., Goodman, W. K., Geffken, G. R., Lewin, A. B., Henin, A., Micco, J. A., Sprich, S., Wilhelm, S., Bengston, M., & Geller, D. A. (2010). A preliminary study of D-cycloserine augmentation of cognitive-nehavioral therapy in pediatric obsessive-compulsive disorder. *Biological Psychiatry, 68*, 1073–1076. https://doi.org/10.1016/j.biopsych.2010.07.015.

Storch, E. A., Wilhelm, S., Sprich, S., Henin, A., Micco, J., Small, B. J., McGuire, J., Mutch, P. J., Lewin, A. B., Murphy, T. K., & Geller, D. A. (2016). Efficacy of augmentation of cognitive behavior therapy with weight-adjusted D-cycloserine vs placebo in pediatric obsessive-compulsive disorder: A randomized clinical trial. *JAMA Psychiatry, 73*, 779–788. https://doi.org/10.1001/jamapsychiatry.2016.1128.

Veale, D., Anson, M., Miles, S., Pieta, M., Costa, A., & Ellison, N. (2014). Efficacy of cognitive behaviour therapy versus anxiety management for body dysmorphic disorder: A randomised controlled trial. *Psychotherapy and Psychosomatics, 83*, 341–353. https://doi.org/10.1159/000360740.

Veale, D., & Neziroglu, F. (2010). *Body dysmorphic disorder: A treatment manual*. West Sussex: Wiley-Blackwell.

Walker, D. L., Ressler, K. J., Lu, K. T., & Davis, M. (2002). Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *The Journal of Neuroscience, 22*, 2343–2351.

Wilhelm, S., Buhlmann, U., Tolin, D. F., Meunier, S. A., Pearlson, G. D., Reese, H. E., Cannistraro, P., Jenike, M. A., & Rauch, S. L. (2008). Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *American Journal of Psychiatry, 165*, 335–341. https://doi.org/10.1176/appi.ajp.2007.07050776. (**quiz 409**).

Wilhelm, S., Phillips, K. A., Didie, E., Buhlmann, U., Greenberg, J. L., Fama, J. M., Keshaviah, A., & Steketee, G. (2014). Modular cognitive-behavioral therapy for body dysmorphic disorder: A randomized controlled trial. *Behavior Therapy, 45*, 314–327. https://doi.org/10.1016/j.beth.2013.12.007.

Wilhelm, S., Phillips, K. A., & Steketee, G. (2013). *Cognitive-behavioral therapy for body dysmorphic disorder: A treatment manual*. New York: Guilford Press.