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A Preliminary Study of D-Cycloserine Augmentation of Cognitive-Behavioral Therapy in Pediatric Obsessive-Compulsive Disorder

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Abstract

Background—Research on the neural circuitry underlying fear extinction has led to the examination of d-cycloserine (DCS), a partial agonist at the NMDA receptor in the amygdala, as a method of enhancing exposure therapy outcome. Preliminary results have supported the use of DCS to augment exposure therapy in adult anxiety disorders; however, no data have been reported in any childhood anxiety disorder. Thus, we sought to preliminarily examine if weight-adjusted DCS doses (25 or 50mg) enhanced the overall efficacy of cognitive-behavioral therapy (CBT) for pediatric obsessive-compulsive disorder (OCD).

Method—Participants were 30 youth (ages 8–17) with a primary diagnosis of OCD. The study design was a randomized, double-blinded, placebo-controlled augmentation trial examining CBT +DCS versus CBT+Placebo (15 youth per group). All patients received 7 E/RP sessions paired with DCS or placebo taken 1 hour prior to sessions.

Results—Although not significantly different, compared to the CBT+Placebo group, youth in the CBT+DCS arm showed small-to-moderate treatment effects (*d*=.31 to .47 on primary outcomes). No adverse events were recorded.

Conclusions—The present results complement findings in adult OCD and non-OCD anxiety disorders and provide initial support for a more extensive study of DCS augmentation of CBT among youth with OCD.

Keywords

Obsessive-Compulsive Disorder; Children; D-Cycloserine; Cognitive-Behavioral Therapy; Treatment; Outcome

Introduction

A potentially significant translational success derived from animal research has shown that the N-methyl-D-aspartate (NMDA) receptor is critically involved in fear extinction, and that the NMDA partial agonist D-cycloserine (DCS) enhances extinction of learned fear [1,2]. The putative ingredient of cognitive-behavioral therapy (CBT) for anxiety is extinction whereby patients are exposed to anxiety-producing stimuli with subsequent response prevention [3]. Based on this formulation and supporting animal research [1,2], studies have supported DCS (50mg taken before exposure sessions) augmentation of exposure therapy in adults with acrophobia [4], social phobia [5,6], and panic disorder [7] with effect sizes for primary outcomes in the medium-to-large range. Among adults with obsessive-compulsive disorder (OCD), Wilhelm et al. [8] showed medium between-group effect sizes in favor of DCS (100mg) (*d*=0.63 and 0.66 at post-treatment and follow-up), while Kushner et al. [9] showed significantly more rapid reduction in obsession-related fear ratings on the Subjective Unit of Distress Scale (SUDS; *d*=0.77). However, groups did not differ in post-treatment SUDS scores or OCD severity. Dosing at 250mg DCS/placebo 4 hours before exposure therapy sessions, Storch et al. [10] showed no significant group differences in OCD severity at post-treatment or in slope of reductions.

We examined the potential benefit of DCS versus placebo augmentation of CBT in pediatric OCD patients given its prevalence rate of 1% [11] and associated impairment [12]. Cognitive-behavioral therapy has demonstrated efficacy for pediatric OCD, but some youth do not benefit and many treatment responders continue to have residual symptoms. Serotonergic medications are efficacious but rarely produce remission [13], may be accompanied by side effects [14], and may not be an acceptable intervention to some parents. Safely enhancing the overall degree of improvement could significantly improve child quality of life and treatment course (e.g., improve treatment compliance).

Method and Materials

Participants

Thirty youth with a principal diagnosis of OCD were recruited across two study sites between February 2007-December 2009. Participant characteristics are presented in Table 1. Inclusion criteria were: 1) Diagnosis of OCD established via an unstructured clinician interview and confirmed with the Anxiety Disorders Interview Schedule for DSM-IV: Parent Version (ADIS-IV-P) [15]. 2) Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)≥16 [16]. 3) Stable on any psychotropic medications for 12 weeks. 4) No comorbid psychosis, bipolar disorder, autism, or substance abuse/dependence. 5) Between 25.0–90.0kg. 6) Received at least one DCS dose. Exclusion criteria included: 1) Presence of primary hoarding symptoms. 2) Having epilepsy, renal insufficiency, or generally poor physical health. 3) Pregnancy or having unprotected sex [in females]. There were no site differences across baseline demographics or clinical characteristics.

Procedures

After obtaining written consent and assent, participants completed study measures, were administered a physical examination by a board certified child psychiatrist, and had lab values assayed (e.g., CBC, metabolic panel, urine toxicology, and pregnancy test [for post-pubescent females]). Thereafter, participants were randomized by a computer-generated program maintained in the site research pharmacy in a double-blinded fashion to CBT+DCS or CBT+Placebo. Assessments were conducted by trained blinded raters at pre-treatment, after session 6, and within one-week post-treatment.

All participants received ten 60-minute CBT sessions based on the Pediatric OCD Treatment Study protocol [13], which includes psychoeducation, cognitive training, and exposure and response prevention (E/RP). Sessions 1–4, which include psychoeducation, cognitive therapy, hierarchy development, and an initial 'easy' exposure (session 4), were held twice weekly. Sessions 5–10, which focus on E/RP, were held weekly. A session interval of ≥5 days was used for exposure sessions because a DCS-free period between administrations maintains the positive effects of DCS on learning and fear extinction [2]. Therapy was provided by experienced therapists supervised by the 1st or 9th authors.

D-cycloserine/placebo were capsulized into 25mg capsules and taken before sessions 4–10. A dosage of 0.7mg/kg corresponds with dosages found in adult studies [4,8] to be effective (50mg/estimated average adult weight of 70kg=.71mg/kg). Accordingly, we kept doses around 0.7mg/kg by using two dosing levels based upon weight ranges: children weighing between 25–45kg took 25mg (0.56–1.0 mg/kg/day) while children weighing between 46–90kg took 50mg (0.56–1.08mg/kg/day). D-cycloserine was taken acutely as there may be significant compensatory changes in the NMDA receptor complex (i.e., chronic down regulation) following chronic administration [17]. Parents gave their children DCS/placebo one hour before psychotherapy sessions 4–10 [8]. There were no documented instances in which DCS/placebo were not taken within one hour (+/−15 minutes) before session.

Measures

The CY-BOCS [16] is a psychometrically sound 10-item semi-structured measure of obsession and compulsion severity over the previous week. The ADIS-IV-P [15] includes a clinician severity rating (CSR) on a 0–8 scale. The CGI-Severity (CGI-S) [18] is a single-item rating of global illness severity. The Multidimensional Anxiety Scale for Children (MASC) [19] and Children's Depression Inventory-Short Form (CDI-Short-Form) [20] measure self-reported anxiety and depressive symptoms, respectively.

Analytic Plan

Data were analyzed with separate 2 (site: Florida, MGH) by 2 (condition: CBT+DCS, CBT +Placebo) by 3 (time: pre-treatment, mid-treatment, post-treatment; Dependent variables: CGI-Severity, CY-BOCS Total Score) or 2 (site) by 2 (condition) by 2 (time: pre-treatment, post-treatment; Dependent variables: ADIS-CSR for OCD, MASC, CDI-Short Form) fixed-effects linear regression with time as the repeated measure. Since there were no group by time by site interactions, we focused on the group by time analysis. There were no missing data. Cohen's *d* was used to examine the magnitude of treatment effects.

Results

Primary Outcomes

Pre-treatment scores on the CGI-S, CY-BOCS, and ADIS-CSR did not significantly differ as a function of group assignment (Table 2). For CGI-Severity ratings, we identified significant main effects for time ($F(2,27)=86.8$; $p<.001$, $d=3.5$) and group ($F(1,28)=6.4$; $p=.02$, $d=0.97$). The group by time interaction was not statistically significant ($F(2,27)=1.5$; $p=.22$); the effect size was moderate in favor of the CBT+DCS arm ($d=0.47$) with a 57% versus 41% symptom reduction.

Using the CY-BOCS, a significant time main effect ($F(2,27)=118.4$; $p<.001$, $d=4.1$) was identified. Neither the main effect for group ($F(1,28)=3.1$; $p=.09$) nor the group by time interaction ($F(2,27)=.69$; $p=.51$) met statistical significance; their effect sizes were moderate ($d=0.66$) and small ($d=0.31$), respectively. The average CY-BOCS reduction for the CBT +DCS arm was 72% versus a 58% symptom reduction for those randomized to CBT +Placebo.

Using the ADIS-CSR, a main effect of time ($F(1,28)=87.6$; $p<.001$, $d=3.5$) was identified. Neither the main effect for group ($F(1,28)=3.0$; $p=.09$) nor the group by time interaction ($F(1,28)=1.2$; $p=.30$) met statistical significance; their effect sizes were moderate ($d=0.65$ and 0.41). Those randomized to CBT+DCS experienced a 71% reduction versus a 53% reduction for those in the CBT+Placebo arm.

Secondary Outcomes

There was no significant group effect or group by time interaction for MASC or CDI-Short Form scores (Table 2).

Adverse Effects

No participant reported adverse effects related to DCS or placebo. CBC, LFTs, electrolytes, BUN, and creatinine were all normal at enrollment and after treatment with DCS.

Discussion

Consistent with adult trials [4–9], children randomized to DCS augmentation of CBT showed moderate treatment effects relative to a placebo control on several symptom severity

indices. D-cycloserine was well-tolerated: no significant DCS-related adverse effects took place and lab values did not change in treated youth. There are several implications of this preliminary study. First, enhancing overall improvement could have substantial quality of life implications during a developmentally sensitive time. Moderate effects sizes consistently in favor of DCS preliminarily suggest the promise of this approach. Second, although SRIs have demonstrated efficacy for pediatric OCD [13], treatment effects are modest and undesirable side effects may occur [14]. Augmenting CBT with DCS may provide a safe alternative for enhancing CBT outcome. Third, many youth with OCD refuse to participate in treatment and/or do not finish a full CBT course. We speculate that attrition may be reduced with a treatment that yields greater effects [8]. Those taking DCS may attempt more challenging E/RP tasks because learning from previous exposure tasks may boost confidence or generalize to other stimuli.

Unlike others' findings in adult OCD [8], analyses of secondary outcomes did not yield significant effects. Although a moderate effect size for reduced depressive symptoms was noted in favor of the CBT+DCS arm, the clinical meaningfulness of this finding seems limited due to truncated range of baseline depressive symptoms. These findings suggest that the mechanism of DCS may be specific to extinction learning, and may not differentially impact non-OCD anxiety or depressive symptoms.

Several limitations warrant comment. First, because this was a preliminary study with multiple goals of evaluating safety, efficacy and feasibility, the sample size was modest and most analyses were underpowered to detect group differences. Second, there was no follow-up period to examine if gains differed when treatment was halted. Third, participants were primarily Caucasian middle-to-high socioeconomic status families. Finally, we could not augment homework assignments with DCS given possible desensitization [17]. There are several areas that warrant further exploration based on these preliminary data: examination of DCS augmentation in a fully powered trial; applying DCS to other pediatric anxiety disorders for which CBT is indicated (e.g., social phobia); and the efficacy of DCS on alternative outcomes (e.g., participant attrition, treatment durability).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant Characteristics

Age	8–17 years	(M = 12.2, SD = 2.8)
Gender	19 Male (63%)	11 Female (37%)
Ethnicity	97% Caucasian	3% Hispanic
Psychiatric Comorbidity	73% at least one DSM-IV-TR Axis I disorder	
ADHD	n = 14	
Generalized Anxiety Disorder	n = 5	
Oppositional Defiant Disorder	n = 4	
Tourette Syndrome	n = 3	
Major Depression	n = 3	
Social Phobia	n = 2	
Enuresis	n = 2	
Specific Phobia	n = 1	
Psychotropic medication	15 (stable dose)	
Selective serotonin reuptake inhibitor	n = 9	
Atomoxetine	n = 2	
Alpha-2 adrenergic agonist	n = 2	
Tricyclic antidepressant	n = 1	
Serotonin norepinephrine reuptake inhibitor	n = 1	
Stimulant	n = 1	

Table 2

Means, Standard Deviations, and Effect-sizes for Outcome Measures for CBT+DCS and CBT+Placebo Treatment Groups

	D-Cycloserine Group (N=15)		Placebo Group (N=15)		Effect Sizes
Measure	**Mean**	**SD**	**Mean**	**SD**	**Cohen's d$^{\Omega}$**
CY-BOCS Total Severity					
Pretreatment	24.1	4.4	26.0	3.8	0.46
Mid-treatment	15.6	6.8	17.9	4.5	0.40
Post-treatment	6.8	6.0	11.0	6.6	0.67
CGI-Severity					
Pretreatment	4.6	0.83	5.1	0.74	0.63
Mid-treatment	3.5	0.92	3.9	0.59	0.52
Post-treatment	2.0	1.0	3.0	1.2	0.91
ADIS-CSR					
Pretreatment	5.1	0.79	5.3	0.70	0.27
Post-treatment	1.5	1.5	2.5	1.8	0.61
MASC					
Pretreatment	41.7	15.4	39.9	13.7	0.12
Post-treatment	31.4	19.7	34.6	14.7	0.19
CDI-Short Form					
Pretreatment	2.6	3.3	3.4	2.8	0.27
Post-treatment	1.4	2.5	2.2	2.1	0.36

SD=Standard Deviation

$^{\Omega}$Between-group Effect Size at each time point using the pooled standard deviation

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