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Short Title: Difficult-to-treat pediatric OCD: DCS Augmented CBT

Difficult-to-Treat Pediatric Obsessive-Compulsive Disorder: Feasibility and preliminary results of a randomised pilot trial of *d*-Cycloserine augmented behaviour therapy

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Abstract

Background: This study examined the feasibility and preliminary effectiveness of D-cycloserine augmented cognitive-behavioural therapy (CBT) for children and adolescents with difficult-to-treat OCD, in a double-blind randomised controlled pilot trial (RCT).

Methods: Seventeen children and adolescents (aged 8–18 years) with a primary diagnosis of OCD, which was deemed difficult-to-treat, were randomly assigned to either nine sessions of CBT including five sessions of DCS augmented exposure and response prevention [ERP+DCS], or nine sessions of CBT including five sessions of placebo augmented ERP [ERP+PBO]. Weight-dependent DCS or placebo doses (25 or 50mg) was taken one hour before ERP sessions.

Results: At post-treatment, both groups showed significant improvements with 94% of the entire sample classified as responders. However, a greater improvement in the ERP+DCS relative to the ERP+PBO condition was observed at 1-month follow-up on clinician rated obsessional severity and diagnostic severity, and parent ratings of OCD severity. There were no changes across time or condition from 1-month to 3-month follow-up.

Conclusions: In this preliminary study, DCS augmented ERP produced significant improvements in OCD severity from post-treatment to 1-month follow-up, relative to a placebo control condition, in severe and difficult to treat pediatric OCD. The significant effect on obsessional severity suggests that DCS augmentation might be associated with enhanced modification of obsessional thoughts during ERP, and warrants further investigation.

Introduction

Cognitive-behavioural treatment (CBT) for pediatric OCD, either alone or in combination with serotonergic reuptake inhibitors (SRI), is only partially effective for the majority of youth. Results from the largest multi-site randomised controlled trial¹ indicates that as many as 60% of children receiving CBT alone, 46% receiving combined CBT and SRI, and approximately 80% receiving SRI alone do not fully remit. For those who do not respond to SRI augmentation of CBT, antipsychotic medications are often prescribed, yet these medications are frequently associated with significant metabolic and endocrine abnormalities and very little is known about their efficacy for pediatric OCD.^{2,3} Significant progress in understanding the underlying neurobiological basis of fear acquisition and extinction, highlights how extinction learning and its clinical translation – exposure and response prevention therapy (i.e., ERP – a major component of CBT) - could be enhanced through specific pharmacological agents that target these neural and cellular pathways. Fear learning and in particular the process of new learning that takes place during exposure therapy is dependent upon neural activity in the amygdala and also involves the neural transmission of glutamate through the N-methyl-D-aspartate (NMDA) receptor.⁴

The anti-tuberculosis medicine D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) agonist, has been shown in rodent and human studies to promote both the extinction of conditioned fear⁵ and the consolidation of learning associated with extinction training,⁶ and furthermore, has improved exposure therapy outcomes in adult studies of acrophobia,⁷ social phobia,^{8,9} and panic disorder.¹⁰ Moreover, given that ERP is the cornerstone of psychological treatments for OCD, there has been three separate trials of DCS augmented ERP in adults with OCD, demonstrating somewhat mixed results.¹¹⁻¹³

Wilhelm et al.¹³ found significant reductions by mid-treatment (i.e., session 5) on OCD severity ratings ($d = 1.17$) with 100mg DCS administered one hour prior to ERP. Furthermore, at post-treatment there were significant between group differences on depression scores ($d = 0.99$) in favour of the DCS group compared with the Placebo (PBO) group. Further, while not significant, between-group effect sizes at post-treatment were large and in favour of the DCS arm relative to the placebo condition on the overall measure of OCD severity ($d = 0.63$). Similarly, Kushner et al.¹¹ found the DCS group reported significantly greater reductions in obsession-related distress compared to placebo ($d = 0.77$) after only four ERP sessions. Of note, DCS was also associated with significantly fewer sessions to achieve clinically significant change, and lower treatment attrition (6% versus 35%), highlighting the favourable effort to benefit ratio of DCS.¹¹ In contrast, Storch et al.¹² found no beneficial effects of DCS (250mg) administered 4 hours before 12 ERP sessions; however, the methodology of this trial differed substantially from Wilhelm et al.¹³ and Kushner et al.¹¹ who administered DCS only one to two hours prior to therapy and in smaller dosages over fewer sessions.¹² These results highlight that DCS may be maximally effective with acute dosing, administered approximately 1 hour before ERP, with beneficial effects occurring early in treatment.¹⁴ The emerging literature consequently provides promising evidence that DCS may be an effective augmentation to ERP and, furthermore, may improve the overall efficiency of ERP, with one study suggesting DCS results in six times faster outcomes in the early stages of ERP treatment.¹⁵

Storch et al.¹⁶ recently examined the effectiveness of DCS augmented ERP in a pediatric OCD sample ($n=30$). Participants were randomized to either CBT+DCS ($n=15$) or CBT+PBO ($n=15$), in which CBT included 7 ERP sessions (i.e., sessions 4-10) paired with DCS or PBO, taken one hour before ERP. Two doses were used, with those weighing 25-45kg taking 25mg DCS (.56 –1.0mg/kg/day) and children weighing 46-90kg taking 50mg

(.56–1.08mg/kg/day). DCS was well-tolerated with no treatment-related adverse reactions. Although not significantly different, participants in the DCS condition demonstrated small to moderately large treatment effect sizes in favour of DCS across post-treatment outcomes ($d=0.67$ on CY-BOCS; $d=0.91$ on CGI severity; and $d=0.61$ on ADIS-CSR).

Given the paucity of research on the role of DCS-augmented ERP in pediatric OCD, combined with evidence that the majority of youth with OCD do not fully recover following current best-practice treatments, we conducted a randomized, placebo controlled double-blind pilot trial of DCS augmented ERP for difficult-to-treat pediatric OCD patients. The development of effective and safe alternatives to augmenting CBT for difficult-to-treat pediatric OCD is crucial, given the limits associated with first line treatment response, coupled with the side-effect profiles of antipsychotic augmentation and patient preferences for non-psychotropic treatment approaches.¹⁷ Thus, children and youth with a primary diagnosis of OCD, considered difficult-to-treat, were randomized to either CBT combined with DCS or CBT combined with PBO in a double-blind pilot trial to establish the feasibility, acceptability and preliminary effectiveness of DCS. The CBT protocol used involved five sessions (i.e., sessions 5-9) of ERP, combined with the corresponding pill (DCS/PBO), administered one-hour prior to session. It was hypothesized that DCS augmented ERP would be associated with greater improvement on OCD symptom severity and functional impairment, as well as improvements on associated anxiety and depression, relative to a placebo control condition.

Method

Participants

Seventeen children and adolescents (seven males; 8–18 years; $M=13.11$, $SD=3.33$ years) with a primary diagnosis of OCD, who were deemed to have difficult-to-treat OCD, were enrolled at Griffith University between May 2009 and September 2010. Difficult to treat

OCD was defined by an initial dose of CBT (6 plus sessions), including adequate ERP, with minimal or no initial response to treatment, reported by parents. Sample size was estimated based on power calculations using published effect sizes from adult studies.^{11,13} Sixteen children were Caucasian (94%) and one youth was of Asian sociocultural background. Inclusion criteria were: (a) a primary diagnosis of OCD, of at least moderate severity (defined by a CY-BOCS score of ≥ 19),¹⁸ (b) at least one parent willing to engage in the treatment, and (c) the child meeting criteria for having “difficult-to-treat OCD” defined as receiving past CBT of at least 6 sessions (range = 6 to >30 sessions), including some degree of session-by-session ERP (either therapist assisted or between session assigned homework), which had not resulted in parent-reported symptomatic change. Thirteen participants (71%) had received CBT and SRI prior to inclusion, and four had received CBT alone. Thirteen youth (76%) were on SRI medication at trial entry. Medication type and dose were stable for at least six weeks prior to entry into the trial (except for one youth who was stable for only 4 weeks prior to entry¹), and remained stable throughout the trial. The duration for which youth had been stable on medication varied considerably at study entry, ranging from 4 weeks (one youth) to 240 weeks, with a mean period of dose stability of 51 weeks (SD = 75 weeks). Five participants (29%) had been hospitalised in the past due to OCD. Exclusion criteria included organic mental disorder; autistic spectrum disorder; medications that were contraindicated with DCS; pregnancy (screened); psychosis; history of seizure; history of other serious medical condition (i.e., cardiovascular, liver, kidney, respiratory abnormalities); serious suicidal risk; concurrent psychotherapy; and suspected impaired IQ (i.e., < 70).

There were eight youth who were screened for eligibility but who were excluded due to the presence of an autistic spectrum disorder (refer Figure S1 CONSORT Flow Diagram available online¹⁹). There were some missing values at an item level within returned self-report measures (less than 10%). Because of this small amount of missing data, it was managed

by replacing missing items with the mean of the other items for that participant at that time of measurement. There was one participant who was not contactable for the 1-month follow-up assessment; however, this participant was re-contacted for the 3-month follow-up.

Sixty-five percent of the sample presented with a secondary comorbid psychiatric diagnosis and 53% presented with a tertiary diagnosis. Table 1 presents participant characteristics and diagnostic information for the sample, including secondary and tertiary diagnoses.

<Table 1>

Design

Children were randomized using a computer-generated list of randomly permuted blocks of pairs, with an allocation of 1:1 to either ERP+DCS (n=9) or ERP+PBO (n=8), with blinding managed by the study pharmacy investigator (Laetitia Hattingh, PhD). All other investigators were blind, as were assessors, therapists and all participants (refer S2 CONSORT Checklist for full details available online ^{19,20}). Pills were compounded to be identical in size and colour, and were dispensed by the study pharmacist corresponding to randomization, prior to session five. The therapist administered each dose to the patient over the five ERP sessions. Treatment involved nine CBT sessions, including 5 sessions of ERP (i.e., sessions 5-9) combined with DCS or PBO. We used a different dose of DCS (25mg or 50mg) dependent on child weight (i.e., <45kg = 25mg, and >46kg = 50mg). The dose was given one hour prior to ERP sessions 5-9. No child was withdrawn from this study as a result of meeting exclusion criteria following blood tests, and all children enrolled in the trial completed treatment, with laboratory tests remaining within normal limits.

Measures

The Anxiety Disorders Interview Schedule for Children–Parent version (ADIS-P ²¹).

The ADIS-P was developed specifically to diagnose anxiety disorders in children, ²² and possesses good inter-rater and retest reliability. The ADIS-P has demonstrated good treatment sensitivity in both childhood anxiety ^{23,24} and OCD. ^{25,26} This interview was administered to the child's parent/s. Each diagnosis receives a Clinician Severity Rating (CSR) based on clinician judgment, scored 0–8, with a score of 4 indicating a clinically significant diagnosis. Inter-rater reliability was conducted across 20% of the video-taped diagnostic interviews by an independent rater, with results indicating excellent reliability (primary diagnosis $\kappa = 1.0$; secondary diagnosis $\kappa = 1.0$; tertiary diagnosis $\kappa = 1.0$).

National Institute of Mental Health Global Obsessive-Compulsive Scale (GOCS & CGI ²⁷). The GOCS consists of a single item measuring global diagnostic severity on a scale from 1 (minimal symptoms) to 15 (very severe). The Clinical Global Impression (CGI) severity scale was used at all assessment points, which rates OCD severity on a single item from 1 through to 7. The GOCS/CGI have demonstrated good to excellent retest-reliability, ^{28,29} and adequate to good convergent validity with the SCL-90 OC scale and the CY-BOCS. ³⁰

Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS ¹⁸). The CY-BOCS is a widely used clinician-rated semi-structured interview that rates severity of obsessions and compulsions across five items: (a) time occupied by obsessions/compulsions, (b) interference from obsessions/compulsions, (c) distress associated with obsessions/compulsions, (d) resistance against obsessions/compulsions, and (e) degree of control over obsessions/compulsions. In addition to separate obsession and compulsion scores, a total severity score is derived from adding all items. The CY-BOCS shows robust reliability and validity properties, such as good to excellent inter-rater agreement, high internal consistency, and construct validity. ¹⁸

*Children's Yale-Brown Obsessive-Compulsive Scale-Parent Self-Report (CY-BOCS-SR*³¹). This parent and child report measure of OCD severity, was developed based on the original CY-BOCS clinician-administered inventory,¹⁸ and both consist of two subscales (five-items each) assessing the distress and impairment caused by obsessions and compulsions. Preliminary studies have supported the psychometric properties of the CYBOC-PR.³¹ These measures were used at each assessment and at the commencement of every session to monitor child's session-by-session progress.

*Multidimensional Anxiety Scale for Children (MASC*³²). This self-report measure assesses anxiety symptoms in children across a number of domains, including physical symptoms, harm avoidance, social anxiety and separation/panic. The MASC is comprised of 39 items assessing frequency of anxiety symptoms/concerns and provides a total anxiety score. It has been found to have good internal reliability and convergent validity.^{32,33}

Adverse Symptoms Checklist (ASC,^{12,16}). Common side effects of DCS (reported at much higher doses for treatment of tuberculosis) include confusion, numbness, tremors, drowsiness, dizziness, difficulty speaking, irritability and headache.⁴² To monitor potential medication-related adverse effects, parents and children were administered an adverse symptoms checklist in line with previous studies,^{12,16} at pre-assessment by the independent evaluator, and at the commencement of every session by the therapist, to monitor symptoms and symptom change following administration of pills at session 5. The ASC is a 30-item checklist that screens for common side effects of medication, including; headaches, constipation, blurred vision, dry mouth. Children and parents rate the child's experience of these symptoms over the past week on a likert-scale from 0 "not at all" to 3 "severe". Monitoring of adverse symptoms commenced from initial contact during assessment phase to establish a baseline of symptoms (child and parent rated symptoms¹⁶). Adverse events were then monitored via weekly completion of the Adverse Events Checklist¹⁶ by youth and

parents, as well as through questioning with parents at the beginning of each session by the therapist. Parent, child and therapist determined whether there had been a change in symptoms following the previous dose of medication by reviewing the completed checklist and discussing symptoms.

Procedures

All procedures used in this study were reviewed and approved through the university human research ethics committee. Following referral into this study, participants were screened via a brief parent interview assessing for obsessive-compulsive symptomatology. If eligible, families attended an assessment conducted by the first author and postgraduate clinically trained clinicians not involved in treatment. At this assessment, written informed consent from parents and assent from children to participate was obtained. Thereafter, the ADIS-P was administered to parents and the CY-BOCS was given to children (including parents whenever appropriate based on clinical judgment). Interviews were conducted at each assessment point (baseline, post-treatment, 1- and 3-month follow-ups). Interviewers were trained in the ADIS-P and CY-BOCS through observation of the first author, followed by close supervision by the first author to maintain integrity. Assessment also included the completion of a number of self-report questionnaires at baseline and post-treatment. Laboratory tests were conducted at baseline to screen for any contraindications of DCS (e.g., complete blood count, metabolic panel, urine toxicology and pregnancy test for post pubertal females) and at post-treatment (excluding pregnancy test and urine toxicology) to monitor adverse events. All children were reviewed at baseline by the consultant psychiatrist (Nigel Collings, MD) for medical contra-indications of DCS and for a prescription of DCS.

Treatment Protocol: The treatment approach³⁴ was a manualized family-based CBT treatment protocol, based on March and colleagues' individual CBT protocol.^{35,36} The treatment involved 9 weekly sessions each running for 1.5 hours, including a brief parental involvement/family review of progress at the beginning and end of the child session (15 minutes beginning and end). There were five trained therapists who delivered treatment to between 1 and 5 clients, and as a result of randomisation, each therapists treated clients across both treatment conditions (with the exception of one therapist who treated only one client – active condition). Therapists were all postgraduate level clinicians with previous experience in CBT for OCD. All clinicians received formal weekly supervision, wherein clinicians reported on client progress, adherence to the treatment protocol, and provided an opportunity to ask questions/problem solve treatment difficulties or process issues. Sessions 1 through 4 included instruction on cognitive-behavioural techniques, including psychoeducation, cognitive training, anxiety management training, monitoring symptoms, developing stimulus hierarchies, and planning for graded ERP. Sessions 5 through 9 involved in-vivo, therapist-assisted ERP, and included the administration of DCS or PBO one hour prior to therapy. At least one session for every participant included ERP occurring in the home context (range was 1 to 3 sessions in total) to assist in generalising ERP effects. Therapists discussed responses to the ASC at the beginning of every session to monitor adverse events, and to query whether any symptom that was endorsed was new, persistent or exacerbated since the last session. All children and parents endorsed the experience of some symptoms from week to week from baseline through treatment (e.g., restlessness, headaches); however, based on the ASC and discussions with parent and child at every session, there were no symptoms reported by child or parent that the therapists deemed treatment-related “adverse events” – defined as new symptoms, with onset during the past week, which were concerning or persistent.

Data Analysis

To examine the equivalence of treatment groups at baseline, an independent samples t -test was conducted for each outcome measure (CY-BOCS, CSR, GOCS, CY-BOCS-SR parent, MASC). Age was also compared using a t -test, and gender was compared using a χ^2 test. For assessing treatment outcome, data were analyzed with separate 2 (Condition: ERP+DCS, ERP+PBO) by 2 (Time: pre-treatment & post-treatment; post-treatment & 1-month follow-up; 1-month follow-up & 3-month follow-up) repeated measures ANOVAs to examine the incremental effects of DCS augmented ERP across time. This data analytic approach was deemed most appropriate for the sample size, to examine incremental effects at each end point, and given that missing data was not an issue. Primary treatment outcome measures were CY-BOCS obsessions, compulsions and total scores, CSR, GOCS and CGI. Secondary treatment outcome measures included the CY-BOCS-SR parent and the MASC. Eta squared (η^2) was calculated to examine the magnitude of the significant time by condition interactions (small effect = 0.009; medium effect = 0.0588; and large effect = 0.1379³⁷), whereas Cohen's d was used to examine the magnitude of the treatment effects between groups.

Results

Baseline Group Differences

Baseline scores for each outcome did not differ significantly as a function of group assignment. Also, there was no age or gender difference in any baseline outcome measure. All children in the sample were deemed difficult to treat – that is, they had previously had treatment (CBT, either alone or in combination with medication) yet continued to experience significant OCD symptoms despite intervention. Interestingly, treatment history was differentially spread across the treatment conditions, with 89% of the DCS group having received past combined treatment of CBT and medication, versus 63% of PBO condition.

Further, the PBO condition had more children (38%, $n=3$) who had previously received CBT alone in the past, versus 10% ($n=1$) of DCS group. Based on the small numbers, analysis of group differences on outcome as a function of different treatment histories was not feasible.

Pre- to Post-Treatment Outcomes

Using repeated measures ANOVA, significant improvements from pre- to post-treatment were found for CY-BOCS obsessions ($F(1,15)=34.55$; $p<.001$), CY-BOCS compulsions ($F(1,15)=44.3$; $p<.001$), CY-BOCS total score ($F(1,15)=40.12$; $p<.001$), CSR ($F(1,15)=31.91$; $p<.001$), GOCS ($F(1,15)=37.3$; $p<.001$), CY-BOCS-SR parent ($F(1,13)=14.76$; $p<.005$), and MASC ($F(1,13)=7.13$; $p<.05$). Yet, there were no significant Condition \times Time interactions. In terms of clinical significance, in the DCS group there was a 100% responder rate (defined by $>25\%$ reduction on CY-BOCS³⁸) compared to 88% responder rate in the PBO condition. In terms of clinical remission (defined by $>50\%$ reduction on the CY-BOC combined with a CY-BOCS score of <14 ³⁸) 56% of those randomized to DCS versus 50% of the PBO condition achieved remission. Refer to Table 2 for means and standard deviations by Condition and across Time on all outcome variables.

<Table 2>

Post-Treatment to 1-Month Follow-Up

There were significant and large Condition \times Time interaction effects from post-treatment to 1-Month follow-up on the CY-BOCS obsessions subscale ($F(1,14)=8.83$; $p<.05$, $\eta^2=.33$; see Figure 1), GOCS scale ($F(1,15)=5.27$; $p<.05$, $\eta^2=.28$), CGI-Severity scale ($F(1,15)=6.60$; $p=.05$, $\eta^2=.18$), and the parent CY-BOCS-SR ($F(1,14)=4.98$; $p=.08$, $\eta^2=.21$) suggesting greater rate of improvement across time for the DCS condition relative to the PBO condition. Post-hoc tests revealed non-significant differences between treatment conditions on mean ratings across measures at 1-month-follow-up; however, inspection of the between group effect sizes revealed meaningful and clinically significant group differences, ranging from 0.26

(small to moderate effect ³⁷) to 0.70 (moderate to large effect ³⁷) (see Table 2). At 1-month follow-up, there was an 89% responder rate in the DCS condition relative to 75% in the PBO condition. In terms of clinical remission, 56% met criteria in the DCS group, whereas 50% met criteria in the PBO condition.

<Figure 1>

1-Month Follow-Up to 3-Month Follow-up

There were no significant Condition \times Time interactions on outcome measures from 1-month to 3-month follow-up. Furthermore, there were no significant main effects of Time, suggesting maintenance of gains across the follow-up period for both groups (see Table 2). At 3-month follow-up, there was an 89% responder rate in the DCS condition relative to an 88% responder rate in the PBO condition. Moreover, in terms of clinical remission, 67% met criteria in the DCS group, whereas 50% met criteria in the PBO condition.

Clinical Significance and Reliable Change at 3 Month Follow-up

Clinical significance and reliable change for each participant across the two groups was further evaluated following recommendations by Jacobsen et al. ^{39,40} Clinically significant change at an individual level was defined as two standard deviations below the mean at post-treatment³⁹ and reliable change was calculated following Jacobsen et al. ^{39,41} reliable change index (RCI) formula, whereby an individual's pre-test mean is subtracted from their post-test mean, divided by the standard error of difference between the two scores.³⁹ Based on these criteria, at 3 month follow-up 89% (n=8) of the DCS group evidenced clinically significant change on the CY-BOCS relative to 75% in the PBO condition (n=6). In regards to reliable change, 89% of both the DCS group and 88% of the PBO group evidenced reliable change on the CY-BOCS from pre to 3-month follow-up based on the RCI.⁴¹ In terms of numbers needed to treat (NNT) at 3-month-follow-up, based on remission rates of 67% versus 50% at 3-month assessment for the DCS condition relative to the PBO condition, the NNT would be 6.

Discussion

The results of this pilot trial demonstrated feasibility for DCS augmented ERP in a pediatric sample. DCS was well tolerated, with no significant treatment-related adverse effects; and moreover, was acceptable to parents, with no refusal to participate in treatment because of DCS. Whilst there were no group differences at post-treatment, the results of this preliminary trial demonstrated large and significant group by time interactions from post-treatment to 1-month follow-up across multiple primary and secondary outcome measures in favor of DCS, suggesting an acceleration of therapeutic gains across time following 5 DCS doses prior to ERP. Although the design of the current trial differed from previous studies, with a reduced number of doses of DCS / PBO (5 doses only, as opposed to 7 doses in Storch et al¹⁶ and 10 doses in previous adult trials^{11,13}), the results of this trial are in line with previous studies which have found support for DCS augmentation, following 5 to 7 doses, when combined with ERP. Interestingly and somewhat different from others¹⁶, it was *following* post-treatment and across follow-up, that effects of DCS were observed. Importantly, in this sample, participants were youth with severe OCD symptomatology, who had received past CBT, often combined with SRI medication, yet were deemed difficult-to-treat in regards to their initial response to treatments. Moreover, almost 30% of this sample had been hospitalized because of their OCD.

The findings of this trial, although non-significant, demonstrated moderate to large between group effect sizes across multiple end points at 1-month follow-up, including d of 0.70 on parent ratings of severity, 0.60 on obsessional severity and 0.50 on overall total CY-BOCS severity. Interestingly, the largest time by group interaction effect from post-treatment to 1 month follow-up was found on obsessional severity ratings, which is consistent with both Wilhelm et al.¹³ and Kushner et al.,¹¹ and may suggest that DCS augmentation is associated

with enhanced modification of obsessions during ERP. At three months follow-up, there remained moderate effect sizes in favour of DCS on obsessional severity ($d = .40$) and total severity ($d = .40$) based on CY-BOCS scores, although these remained non-significant. Of note, from 1 month to 3 months follow-up, there were no further significant interactions of time by treatment, nor was there a significant main effect of time, suggesting stability across measures of outcome and across treatment conditions, albeit smaller between group effect sizes at longer term follow-up. These findings suggest that DCS was associated with greater improvement relative to the PBO condition over a 1-month period following treatment, but not beyond. This finding has important implications in terms of the specific role DCS might play in enhancing behavior therapy outcomes, such that an initial increased speed of change might lead to a reduction in the amount of therapy required and could also be associated with less attrition; however, further research is needed to examine intensive approaches, as well as explore ways in which to leverage the observed enhancement effect beyond 1 month follow-up. Indeed in this trial, the length of treatment was arguably brief by clinical standards, particularly when we consider that the current sample was deemed difficult-to-treat. For example, past trials of CBT for pediatric OCD have involved 16 sessions of CBT (14 weekly, plus 2 booster sessions⁴³), almost double that delivered in this trial, providing support for the improved therapeutic efficiency of DCS on ERP outcomes.

Kushner et al.¹¹ and Chasson et al.¹⁵ argue that DCS enhances ERP outcomes through increasing efficiency, particularly in the early stages of treatment, or rather, after the first four or five sessions of DCS combined ERP (i.e.,^{11,13}). Kushner et al.¹¹ found that participants in the DCS arm achieved clinically significant symptom reduction faster than those in the PBO arm, in approximately two sessions less, and moreover, were about one-sixth less likely to drop out of treatment. Similarly, Chasson et al.¹⁵ demonstrated that participants in Wilhelm et al.'s¹³ adult OCD trial experienced a more rapid treatment response with DCS, with a six-fold

increase in symptom reduction during early stages of therapy relative to PBO. In our trial, we based our design on these earlier studies, incorporating only five doses of DCS / PBO with five sessions of ERP in the final stages of CBT (session 5 through 9). Our results suggest that DCS may assist in accelerating outcomes following treatment completion, which would be expected if DCS has an ameliorating effect on learning acquired during extinction or exposure therapy. Improved treatment efficiency and durability may provide enormous clinical benefits, including substantive reduction in therapy costs, greater access to therapy and retention of clients, and a reduction of strain and long term financial burden on our health services. Research specifically examining the efficacy of DCS augmented *intensive* treatments is necessary in order to scientifically address these questions regarding the clinical utility of DCS.

The clinical parameters around optimizing DCS augmentation are currently limited. Very recent animal⁴⁵ and human⁴⁶ studies have demonstrated that positive augmentation effects are moderated by *successful* exposure therapy during psychotherapy sessions, that is, significant within session reduction of SUD's. These findings suggest that DCS has benefits for those patients who experience substantive within session extinction of fear, and suggest that future studies might focus on administering DCS post-session, only after successful ERP and reduction of fear, or alternatively, use DCS during prolonged sessions, whereby sessions end once habituation or extinction is achieved. The cumulative evidence, albeit preliminary, provides promise for the clinical benefits of DCS; however, ongoing research, using novel design and methodology is needed in order to further clarify the critical parameters for optimizing the clinical benefits of DCS augmentation.

Given that a large proportion of youth with OCD are treatment refractory following first line treatments, there is a pressing need to find effective, efficient and safe alternatives to augmenting CBT and SRI interventions. Currently, antipsychotic augmentation is widely prescribed for refractory OCD, yet there are no efficacy data, side effects profiles are not

favourable, and parents are frequently reluctant to medicate their children with these drugs.¹⁷ This preliminary investigation of difficult-to-treat OCD suggests that DCS augmented exposure therapy may provide an acceptable, efficient and therapeutically effective adjunct to first-line treatments; however, further large scale RCTs are necessary in order to inform evidence-based practice parameters.

This study is not without limitations. Most notably, the sample size was modest, and therefore analyses were powered to detect only large group differences. The sample size also did not allow for analysis of potential moderators of treatment response (e.g., comorbidity, OCD symptom subtypes). Further, the groups did differ in terms of the nature of their treatment history (i.e., CBT alone or combined treatment). Moreover, medication stability of at least 6 weeks at study entry was brief relative to other trials,¹⁶ and therefore maximum dose effects may not have been fully achieved by at least one youth, which presents a potential confound in the outcomes presented here. Furthermore, the sample was predominantly Caucasian and mid-to-high socio-economic status, limiting generalization. There was no long-term follow-up beyond three months, therefore the results are limited in terms of understanding the durability of treatment effects and possible benefits of DCS on longer term functioning. And finally, the nature of our design does not allow for an examination of differential dose effects of DCS; that is, whether additional sessions of DCS augmented ERP (beyond 5 doses) would have been associated with larger between group effect sizes, or further improvement beyond one-month follow-up. Innovative dose-response designs are needed to further clarify the precise dose related responses associated with augmented ERP.

Conclusions

This study offers a valuable contribution to the literature in being the only preliminary investigation published to date examining a novel treatment for difficult to treat pediatric OCD. Furthermore, a pilot study of this nature is an essential step towards the advancement and

refinement of new technologies and procedures.⁴⁴ Results of pilot studies such as this are necessary to support more expensive and pivotal efficacy trials. The results provide support for the feasibility, acceptability and effectiveness of DCS augmented ERP in a severe and difficult-to-treat sample of children and youth with OCD and furthermore, serves to inform the field of the need for a larger efficacy trial. The potential of DCS as an effective augmentation agent to ERP is one that has numerous benefits, including safety, acceptability, reducing therapy dropouts and curtailing treatment costs. Further research including large randomized clinical trials of efficacy, as well as experimental studies aimed at examining the underlying mechanisms of DCS are warranted and will move the field forward in terms of developing treatment guidelines and informing clinical practice.

Footnotes

1 Analyses were conducted with and without this participant, given that the medication was not stable 6 weeks prior to study entry; however, analyses did not vary as a result of removing this participant. Therefore, all data points for this participant were retained.

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Table 1. Participant Characteristics

Age	8-18 years, M=13.11, SD=3.33
Gender	7 male (41%), 10 female (59%)
Ethnicity	16 Caucasian (94%), 1 Asian (6%)
Psychiatric Comorbidity	65% secondary diagnosis, 53% tertiary
Specific Phobia	3
GAD	8
MDD	2
SAD	1
Social Phobia	3
PTSD	1
ADD/ADHD	4
SRI Mediation - Current	13 (76%)
Treatment History	
CBT	4
CBT + SRI	13 (76%)
Past Hospitalisation	5 (29%)

Note: GAD: Generalised Anxiety Disorder; MDD: Major Depressive Disorder; SAD: Separation Anxiety Disorder; PTSD: Post-Traumatic Stress Disorder; ADD/ADHD: Attention Deficit Disorder/Hyperactivity Disorder; SRI: Serotonergic Reuptake Inhibitors; CBT: Cognitive Behaviour Therapy.

Table 2. Means and Standard Deviations across Treatment Conditions and Outcomes at Pre- and Post-Treatment and One- and Three-Month Follow-up

Measure	Pre Treatment		Post Treatment		Cohen's d Pre - Post Condition	1 Month Follow Up		Cohen's d Post - 1 Month Condition	3 Month Follow Up		Cohen's d 1 - 3 Month Condition
	DCS	Placebo	DCS	Placebo		DCS	Placebo		DCS	Placebo	
CSR	6.89 (0.78)	6.38 (1.06)	2.87 (2.6)	2.60 (2.2)	0.11	2.13 (1.87)	2.75 (2.21)	0.30	2.67 (2.29)	3.38 (1.67)	0.35
GOCS*	10.78 (2.1)	10.25 (1.8)	6.11 (2.73)	5.00 (2.39)	0.43	5.20 (1.70)	5.75 (2.40)	0.26	5.00 (2.20)	5.13 (2.70)	0.22
CGI- Severity*	5.67 (0.70)	5.38 (0.7)	3.00 (1.65)	2.63 (1.30)	0.25	1.89 (0.84)	2.63 (1.51)	0.61	1.89 (0.90)	2.13 (1.13)	0.23
CY-BOCS* Obsession	14.89 (2.75)	14.50 (2.97)	7.11 (2.26)	6.65 (4.06)	0.15	5.43 (2.07)	7.38 (4.14)	0.60	4.67 (3.00)	6.13 (4.51)	0.40
CY-BOCS Compulsion	15.11 (2.76)	14.38 (2.97)	6.67 (3.12)	7.13 (3.94)	0.13	5.57 (1.90)	6.50 (3.60)	0.32	6.00 (4.10)	6.88 (2.90)	0.25
CY-BOCS Total	30.0 (5.47)	28.88 (5.8)	13.78 (5.3)	13.75 (7.70)	0.00	11.00 (3.90)	13.88 (7.18)	0.50	10.14 (7.69)	13.00 (6.76)	0.40
CY-BOCS- SR Parent*	27.44 (6.63)	23.29 (7.34)	12.29 (7.08)	12.50 (8.63)	0.15	9.43 (5.7)	13.75 (6.70)	0.70	13.78 (9.15)	12.00 (7.30)	0.22
MASC	44.00 (21.43)	62.25 (17.97)	27.00 (25.93)	47.14 (31.64)	0.70	-	-	-	-	-	-

Note: DCS = d-Cycloserine; PBO = Placebo; CSR = clinician severity rating, based on ADIS-P interviews; GOCS = National Institute of Mental Health Global Obsessive-Compulsive Scale; CGI = National Institute of Mental Health Clinical Global Impression -Severity Rating; CY-BOCS obsession = Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) obsessional severity rating; CY-BOCS compulsion = CY-BOCS compulsion severity rating; MASC = Multidimensional Anxiety Scale for Children; CY-BOCS-SR Parent = CY-BOCS Self Report Parent Version. Cond. = Treatment condition.

* Significant time by treatment condition interaction, post to 1 month follow-up, $p < .05$; CY-BOCS SR Parent $p = .08$

Figure 1. Significant Time by Condition Interaction on Children's Yale-Brown Obsessive-Compulsive Scale Obsessional Severity

Note: DCS = D-cycloserine; PBO = Placebo