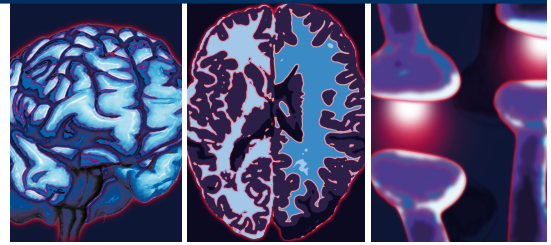


MANAGEMENT PERSPECTIVE



Advances in the treatment of pediatric obsessive–compulsive disorder: rationale and design for the evaluation of D-cycloserine with exposure and response prevention

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Practice points

- Obsessive–compulsive disorder (OCD) is a prevalent condition among children and adults that causes considerable distress, disability and impairment.
- Cognitive-behavioral therapy with exposure and response prevention (E/RP) and serotonin reuptake inhibitor medications are evidence-based treatment options for youths and adults with OCD.
- While E/RP and serotonin reuptake inhibitors produce significant reductions in obsessive–compulsive symptom severity, youths frequently remain symptomatic after either of these treatments.
- D-cycloserine (DCS) is an augmentative agent that has been shown to play a pivotal role in fear learning and fear extinction processes.
- E/RP augmented with DCS has shown promise in adult OCD and anxiety patients, with patients showing a more robust and rapid reduction in symptom severity compared with placebo.
- For pediatric OCD, a preliminary investigation suggested that DCS-augmented E/RP resulted in enhanced reductions in obsessive–compulsive symptom severity relative to placebo.
- A large-scale randomized placebo-controlled trial is underway to further investigate the efficiency, efficacy and tolerability of DCS-augmented E/RP in pediatric OCD.
- Findings from this trial are pivotal to determining the efficacy, safety and tolerability of DCS-augmented E/RP for youths with OCD prior to its mainstream clinical application.
- This clinical trial and its findings may modify current treatment practices by providing evidence of a safe option for enhancing the efficacy of an empirically supported psychotherapy (e.g., E/RP).

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SUMMARY Exposure-based cognitive-behavioral therapy and serotonin reuptake inhibitor medications are efficacious treatment options for the management of pediatric obsessive–compulsive disorder. Despite established efficacy, many youths receiving either therapy remain symptomatic after acute treatment. Regardless of the rationale for persistent symptoms, a clear need emerges for treatment options that restore functioning efficiently to symptomatic youths. One innovative approach builds upon the identified role of NMDA receptors in the fear extinction process. Instead of breaking existing connections during fear extinction, new associations develop that eventually predominate over prior associations. Recent investigations have explored augmenting exposure-based cognitive-behavioral therapy with the NMDA partial agonist D-cycloserine, with preliminary results demonstrating expedited treatment gains and moderately larger effects above exposure and response prevention therapy alone. A large randomized clinical trial is underway to evaluate the efficacy and efficiency of this therapeutic combination in pediatric obsessive–compulsive disorder. Results from this trial may translate into improved management practices.

Obsessive–compulsive disorder (OCD) is a prevalent neuropsychiatric disorder impacting 1–2% of youths [1,2], and represents one of the leading causes of disability in the developed world [3]. Its hallmark symptoms of obsessions and compulsions cause considerable distress and impairment [4–6], and result in diminished quality of life [7]. Without treatment, obsessive–compulsive symptoms that start during childhood are likely to persist into adulthood, highlighting the need for timely intervention. Presently, two treatments have demonstrated efficacy for reducing obsessive–compulsive symptoms in children with OCD: exposure-based cognitive-behavioral therapy (CBT) and serotonin reuptake inhibitors (SRIs). CBT includes multiple components such as psychoeducation, cognitive restructuring and parental involvement. While there is some support for utilizing only cognitive components in adults [8], the core therapeutic component in CBT for youths is exposure and response prevention (E/RP). E/RP requires youths to repeatedly encounter situational and/or internal anxiety triggers. While completing these exposures, youths must learn to resist engaging in compulsions until habituation to the anxious state is achieved. For youths receiving medication management, treatment commonly involves SRI medications that encompass a specific tricyclic antidepressant (i.e., clomipramine), and selective serotonin reuptake inhibitors (SSRIs). Currently four SRI medications have been approved by the US FDA for the treatment of youths with OCD (i.e., clomipramine, fluvoxamine, fluoxetine and sertraline). Pooled effects suggest that E/RP may have some advantage over SRI treatment alone [9,10] leading to clinical standards that recommend children with mild-to-moderate obsessive–compulsive severity initially receive

E/RP alone, whereas those with moderate-to-severe symptoms should receive E/RP with SRI therapy [11,12].

Difficulty implementing current treatment recommendations

Presently, there are several challenges that stymie the implementation of recommended practice parameters. First, the gains produced by E/RP, while substantial, infrequently achieve levels of symptom remission. In the largest study of exposure-based psychotherapy for pediatric OCD, remission rates for youths receiving E/RP alone, E/RP + SSRI and SSRI alone were 39, 53.6 and 21%, respectively [11]. This indicates that somewhere between 61 and 79% of youths receiving monotherapy treatment and 46% of those receiving combined treatment remained symptomatic after acute treatment. Second, attrition poses a challenge for E/RP as 11–25% of children and families discontinue treatment prior to completing a full protocol [11,13,14]. Early discontinuation may result from difficulty participating in exposure-based therapy, treatment burden and/or a perceived lack of immediate therapeutic benefit. Third, and perhaps most concerning, there are a limited number of therapists who are trained to treat pediatric OCD [15,16]. Given the inaccessibility of evidence-based psychotherapy, medications are commonly relied upon to treat obsessive–compulsive symptoms in youths regardless of severity. Although SRI medications have demonstrated significant reductions in obsessive–compulsive symptom severity (see [17] for a review), SRI monotherapy rarely results in symptom remission [11], and may be accompanied by side effects and less frequent serious adverse events (e.g., behavioral activation) [18–20].

Enhancing treatment outcomes

Various augmentation and enhancement strategies for both medication and psychotherapy have been explored to improve outcomes. For patients who demonstrate only a partial response to an adequate trial of SRI monotherapy, a trial of sufficient length at therapeutic dosage with another SRI followed by augmentation with another psychiatric medication has been recommended [12,21,22]. Augmentation with other pharmacological agents such as atypical antipsychotics [23], clomipramine [24] and benzodiazepines [25] has been investigated in controlled trials. While there is some evidence to support antipsychotic augmentation in adults with OCD (i.e., risperidone and quetiapine) [23], controlled antipsychotic augmentation trials are lacking in youths. Moreover, these approaches may be associated with adverse behavioral, metabolic and cardiovascular effects [26] (see [27] for a safety review of antipsychotics in pediatric and adolescent patients).

Aside from medication augmentation approaches, there has been investigation into the added benefit of E/RP for youths who exhibit only a partial response to SRI monotherapy medication. Results from one randomized clinical trial indicate that the addition of E/RP produces more treatment responders (69%) than medication alone (30%) [28]. Despite the efficacy of E/RP, dissemination has lagged, at least in part, owing to the limited accessibility of trained therapists. To address this, alternative strategies to weekly in-office therapy have been explored (e.g., intensive approaches [13,29] and telehealth-based administration [30]). While preliminary investigations have demonstrated efficacy, these approaches primarily focus on improving access to evidence-based psychotherapy and do not directly address the limited availability of trained practitioners. Moreover, these approaches do not necessarily enhance efficacy (or decrease the number of visits) beyond that observed with traditional weekly in-office therapy [13], and may even present additional barriers (e.g., costs relocating for intensive therapy, families purchasing computer equipment and legal barriers such as providing treatment across state lines). Thus, there is a clear need for innovative approaches to safely optimize treatment outcomes in pediatric OCD.

Emerging findings from translational research presents a promising augmentation strategy to enhance therapeutic outcomes from E/RP.

These findings demonstrate that NMDA receptors found in the amygdala and medial prefrontal cortex play a critical role in fear extinction [31,32] (see [33] for a detailed review of NMDA receptors and fear extinction). Several studies have examined the use of the NMDA partial agonist, D-cycloserine (DCS), to facilitate the functioning of NMDA receptors thereby enhancing fear extinction and extinction retention [34–37]. DCS is an antibiotic that has been FDA-approved as a treatment for tuberculosis. Evidence suggests that DCS facilitates extinction by blocking the extinction-impairing effect of a corticosteroid synthesis inhibitor and enhancing the extinction-facilitating effects of a synthetic glucocorticoid [33,38]. During this process, fear-extinction studies indicate that neural associations between feared stimuli and conditioned responses are not broken or forgotten during the extinction process, but rather new associations are formed that eventually predominate over prior associations. Stated another way, fear extinction does not erase the initial fear memory, but instead results in active learning that suppresses the original fear memory. As fear habituation and extinction learning are cornerstones of E/RP, the administration of DCS alongside E/RP holds promise for accelerating the fear-extinction process that occurs in exposure-based psychotherapy.

In non-OCD anxiety disorders (e.g., acrophobia, social phobia and panic disorder), adults who received both DCS and exposure therapy demonstrated significantly greater reductions in target fear symptoms compared with individuals who received placebo and exposure-based therapy [39–42]. Specifically, for adults with OCD, three randomized, placebo-controlled trials have been published that compare the augmentation of E/RP with either DCS or placebo. Wilhelm *et al.* randomized 23 participants to either placebo or 100 mg DCS 1 h before each of ten E/RP sessions [43]. Group differences emerged at mid-treatment in favor of the DCS participants ($d = 1.17$). Effect sizes were large and favored DCS ($d = 0.63$ and 0.66 at post-treatment and follow-up) and participants receiving DCS showed response to therapy two-times faster than those receiving placebo [44]. Although findings were not statistically significant at post-treatment or 1-month follow-up, there was limited power to detect between-group differences. Kushner *et al.* randomized 32 participants to receive either placebo or 125 mg DCS 2 h prior

to each of their ten E/RP sessions [45]. Relative to placebo, the decline of obsession-related fear on the Subjective Unit of Distress Scale was significantly faster among participants receiving DCS ($d = 0.77$). Moreover, the DCS group required two fewer sessions than did the placebo group to attain a >50% Subjective Unit of Distress Scale reduction on all hierarchy items. However, groups did not significantly differ on the Yale–Brown Obsessive Compulsive Scale scores at post-treatment. Finally, Storch *et al.* randomized 24 adults with OCD to receive either placebo or 250 mg DCS 4 h prior to 12 E/RP sessions [46]. No significant differences on the Yale–Brown Obsessive Compulsive Scale were identified at post-treatment ($d = -0.19$), nor did the groups differ significantly in rate of reductions across the session. As the critical period of DCS augmentation is hypothesized to take place not during the exposure session, but afterward during the period of memory consolidation [43], methodological differences (e.g., timing of DCS and dosage) may account for the null findings observed in this trial. Collectively, the three trials for adults with OCD used similar methodologies and demonstrate support for the benefit of E/RP augmented with DCS relative to placebo.

While results are promising in adults, there has been only one published examination of DCS in pediatric OCD. This pilot study by Storch and colleagues utilized a randomized, double-blinded, placebo-controlled trial in which 30 youths with OCD received either placebo, 25 or 50 mg of DCS (depending on weight) 1 h before E/RP sessions [47]. Compared with the placebo group, youths receiving DCS showed reduced obsessive–compulsive symptoms at post-treatment on the Children’s Yale–Brown Obsessive Compulsive Scale (CY-BOCS; $d = 0.66$). The average CY-BOCS symptom reduction for youths receiving DCS was 72 versus a 58% reduction for those receiving placebo. Taken together, the addition of DCS to E/RP appears to offer a promising augmentative strategy for pediatric OCD patients to produce moderately larger effects above E/RP therapy alone.

Evaluating DCS with CBT for pediatric OCD

While the combination of DCS with exposure therapy has not yet entered mainstream use due to conclusive efficacy studies not yet being completed, its preliminary support warrants further

investigation. Building from promising findings, a collaborative R01 grant was funded by the National Institute of Mental Health (Principal Investigators; EA Storch and DA Geller) to evaluate the efficacy of DCS in a large-scale, randomized, placebo-controlled trial in pediatric OCD. The primary intent of the study is to determine whether DCS augments the short-term efficacy of E/RP to a greater extent than placebo by producing a greater and/or more rapid reduction in obsessive–compulsive symptom severity. Ancillary aims of this investigation include safety/tolerability of DCS in youths and maintenance of response over the subsequent 6 months.

Study design

In this study, 150 youths between the ages of 7 and 17 years with OCD are randomly assigned to one of the two treatment conditions: E/RP with DCS or E/RP with placebo. Seventy five youths will be enrolled in each study arm. Recruitment sites include the University of South Florida (FL, USA) and Massachusetts General Hospital/Harvard Medical School (MA, USA). Participant eligibility for the study involve a multigate recruitment protocol, similar to that used in the Pediatric OCD Treatment Studies [11,28]. Inclusion and exclusion criteria for study participation are detailed in [Table 1](#). After parental informed consent and child assent are obtained, families are invited to complete a detailed screening to fully assess study eligibility (see [Table 2](#) for detailed list of measures and assessment schedule). Those families determined to be eligible are screened 7 days later for a baseline visit to assess primary and secondary measures.

Treatment protocol

Following the baseline visit, participants receive ten sessions of psychotherapy over 8 weeks. An abbreviated therapy protocol was selected as, if effective, it would likely reduce the burden experienced by patients, families and therapists and offer easier dissemination in clinical settings. Therapy sessions 1–4 occur during the first 2 weeks, and sessions 5–10 will take place weekly. Based upon an empirically supported treatment manual [11], therapy sessions 1–3 focus on psychoeducation, cognitive therapy and developing a fear hierarchy, while sessions 4–10 focus on conducting E/RP in a hierarchical fashion. Study therapists’ training included attendance of a 2-day training workshop, observation

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Rationale
Age 7–17 years inclusive	Matches developmental sensitivity of treatments and measures
Primary or coprimary diagnosis of OCD using the K-SADS-PL and all available information [54]	Disorder of interest
CY-BOCS total score ≥ 16	Suggests a moderate level of obsessive–compulsive symptom severity
IQ ≥ 85 on the WASI	Ensure that results apply to a wide range of children, while still ensuring that children are able to actively participate and understand therapists' instructions
English speaking	Study therapists are only able to conduct CBT in English
Exclusion criteria	Rationale
Receiving concurrent psychotherapy	Confounds internal validity. Families will have the option to discontinue other services to enroll in the study
Failed response to a previous adequate trial of exposure-based CBT for OCD	Confounds internal validity. If failed to respond to CBT in the past, CBT may not be an appropriate treatment. Also unsystematic sampling bias
No new treatments and/or fluctuations in existing medication dosage	Confounds internal validity. Established psychotropic medications must be stable at least 8 weeks (6 weeks for antipsychotics) prior to study enrollment with no planned changes during study participation
Clinically significant suicidality or suicidal behaviors within the past 6 months	May require additional or different treatments. Patient will be referred to appropriate clinical care
Diagnosis of conduct disorder, autism, bipolar, schizophrenia, schizoaffective disorders or substance abuse in the past 6 months.	May require additional or different treatments
Youth with primary hoarding symptoms	Confounds internal validity. Hoarding OCD may be conceptually and genetically different from other subtypes of OCD [55], and may be excluded from OCD in the DSM-V [56]
Weight <25.0 kg	Safety
Epilepsy, renal insufficiency and current/past history of alcohol abuse	DCS is contraindicated
Pregnant or having unprotected sex (in females)	Effects of DCS on pregnancy are unknown
Presence of a significant and/or unstable medical illness that may lead to hospitalization during the study	May require additional or different treatments. Also, significant medical condition may limit the child's ability to participate in therapy and complete study assessments
Known allergy to DCS	Safety

CBT: Cognitive-behavioral therapy; CY-BOCS: Children's Yale–Brown Obsessive Compulsive Scale; DCS: D-cycloserine; DSM-V: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; IQ: Intelligent quotient; K-SADS-PL: Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime; OCD: Obsessive–compulsive disorder; WASI: Weschler Abbreviated Scale of Intelligence.

of videotapes of expert therapists conducting treatment (EA Storch and S Wilhelm) and completion of training cases under the supervision of expert therapists. As a final assurance of treatment integrity, all therapy sessions are audio recorded with 20% of sessions being randomly selected for rating of treatment adherence.

DCS dosing & adverse effects evaluations

Randomization to DCS or placebo will occur prior to session 4, corresponding with the start of E/RP sessions. Similar to past studies [43,45,47], the dosing of DCS/placebo will take place 1 h prior to E/RP sessions (sessions 4–10). Both the placebo and DCS medication are provided by the institutions' research pharmacy, and are

matched for size, color and taste. Medication dosing (25 or 50 mg) will be based upon weight ranges to ensure that participants have comparable mg/kg levels. Children weighing between 25 and 45 kg will be given a dosage of 25 mg, and children ≥ 46 kg will be given 50 mg provided in two 25 mg capsules. Adverse effects from DCS/placebo will be systematically reviewed at weekly visits using the Safety Monitoring Uniform Report Form [48].

Assessment training

All study staff are blind to whether the participant is receiving DCS or placebo. Throughout the course of treatment, the CY-BOCS is administered at every other therapy session by

Table 2. Study visit and assessment schedule.

Procedures	Screening	Baseline	Session 2	Before CBT session 4	Mid-treatment	Session 8	Post-treatment	Follow-up assessments	Ref.
	Week 0	Week 1	Week 2	Week 3	Week 6	Week 8	Week 10	1-, 3- and 6-months	
KSADS-PL	X								[69]
CY-BOCS [†] ; CGI-S [†]	X	X	X	X	X	X	X	X	[60,64,65]
CDRS; FAS; COIS; CIS; PedsQL; MASC; OCI-CV; CBCL		X		X	X		X	X	[57,58,61,62,67,70–72]
CGI-I				X	X		X	X	[59]
Extinction paradigm		X							[74]
ERQ		X			X				[66]
CSQ; HPI							X		[63,68]
TAS					X		X		[73]
Exam, laboratory and pregnancy tests [‡]	X						X [‡]		[47]

[†]Administered every second therapy session.

[‡]Laboratory tests are obtained at screening and post-treatment.

CBCL: Child Behavior Checklist; CBT: Cognitive-behavioral therapy; CDRS: Children's Depression Rating Scale-Revised; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impressions-Severity; CIS: Columbia Impairment Scale; COIS: Child Obsessive Compulsive Impact Scale; CSQ: Client Satisfaction Questionnaire; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; ERQ: Expectancy Rating Questionnaire; FAS: Family Accommodation Scale; HPI: Hierarchy Progression Index; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; MASC: Multidimensional Anxiety Scale for Children; OCI-CV: Obsessive Compulsive Inventory-Child Version; PedsQL: Pediatric Quality of Life Inventory; TAS: Therapist Alliance Scale.

independent evaluators (IEs). The study IEs' training included didactics about study measures led by expert raters (DA Geller and EA Storch) and rater certification. Ongoing training to ensure cross-site consistency will continue through IEs regular participation in cross-site teleconference calls led by an expert rater (DA Geller). As a final assurance of rating consistency and integrity, all assessment sessions are audio-taped with 20% of sessions being randomly selected to assess reliability and integrity.

Treatment outcome evaluation

At the end of week 10, participants are evaluated to determine current symptom severity and treatment outcome. The primary outcome is the change in obsessive-compulsive symptom severity as assessed by IEs on the CY-BOCS. For categorical secondary outcomes, response is defined as a Clinical Global Impression-Improvement rating of 'much improved' or 'very much improved', while remission is defined as CY-BOCS ≤ 10 . As clinical management often requires treatment to last longer than typical 10-week efficacy trials, responders at week 10 are followed for up to 6 months to examine the durability of acute treatment gains.

Conclusion & future perspective

Presently, the research base on DCS in pediatric OCD (or other psychiatric conditions) is

premature to warrant changes to the recommended standard of clinical care; however, forthcoming findings from the abovementioned trial, as well as other ongoing studies, carry potentially significant implications that may result in modifications to current management practices. First, preliminary evidence suggests that patients receiving DCS with E/RP obtain expedited treatment gains compared with patients receiving E/RP alone. Given the limited number and availability of trained practitioners, the acceleration of OCD symptom reduction with DCS holds considerable importance related to reduced strain on finite clinical resources. Consequently, reduced session burden may increase the availability of trained E/RP therapists and result in more youths receiving treatment. Second, preliminary evidence suggests that youths treated with DCS and E/RP exhibit greater reductions in obsessive-compulsive symptom severity relative to placebo [47]. As many youths remain symptomatic after acute treatment with either evidence-based approach (E/RP or SRI), it is important to investigate safe and tolerable treatment options that may enhance chances at symptom remission. Indeed, youths taking DCS may attempt more challenging E/RP tasks later in treatment due to quicker reductions in fear to stimuli attained early in treatment. These expedited reductions may not only boost patient confidence with exposures, but may also generalize

to other stimuli to facilitate greater symptomatic reductions. Third, DCS augmentation of E/RP may have carry-over effects to help reduce attrition rates. For example, patients often report discontinuing treatment due to the perceived time burden associated with psychotherapy and perceived ineffectiveness [49]. Moreover, parents who are involved in the treatment of youths may miss work days to accommodate their child's obsessive–compulsive symptoms and/or take their child to appointments. As E/RP sessions augmented with DCS may assist youths with habituation to feared stimuli in a more efficient and effective manner, children and families may achieve response more quickly, shortening the time and cost burden associated with a full course of E/RP treatment. Finally, optimizing E/RP with DCS may likely lessen functional impairment in pediatric OCD and improve the overall quality of life. Thus, the combination of DCS and E/RP carries the potential to overcome some of the current challenges that impede E/RP monotherapy.

Forthcoming and positive findings from the ongoing trial (and others in different neuropsychiatric conditions) may influence current management practices in several ways. First, the clinical utilization would necessitate increased collaboration and communication between prescribing psychiatrists and treating psychologists. Because adequate and timely dose administration alongside E/RP is needed to facilitate fear extinction, regular communication becomes increasingly important. Second, beyond modifying the pragmatics of monoclinician treatment, the utilization of DCS with E/RP may help therapists maximize limited clinical resources (e.g., time) so as to make E/RP treatment more available. Third, the use of DCS with E/RP may present a safe and tolerable treatment alternative for difficult-to-treat cases considering therapeutic augmentation with an antipsychotic medication. Underlying current management practices, as well as these potential changes, is the need for ongoing assessment of youth's symptom severity with empirically validated measures (see [50] for a comprehensive review). Regular assessment in treatment is important to determine whether youth are responding to treatment and/or whether different treatments should be considered. While holding much promise, novel augmentative strategies are not without their own challenges. The emphasis of the abovementioned study is to

examine the efficacy, efficiency and tolerability of DCS with E/RP in pediatric OCD. Pending positive results, a feasibility trial in the community is warranted to facilitate the implementation and dissemination of these management practices into regular clinical care.

As scientific research progresses, neuroscientific findings are playing a key role in providing new information that informs clinical research and practice. Although pertinent to OCD, many other areas of treatment research are integrating the findings that DCS enhances inhibitory learning mechanisms into their treatment paradigms. For example, several studies are employing related methodology and utilizing DCS to enhance therapeutic outcomes in drug addictions [51], smoking cessation [52] and post-traumatic stress [53]. Indeed, the transdisciplinary model of treatment research carries wide-spread implications for treatment of patients across mental health conditions. In summary, the novel therapeutic approach of combining DCS with E/RP may change pharmacological and psychotherapeutic management of pediatric OCD. Findings from this multisite study are pivotal to demonstrating that DCS augmentation of E/RP is a safe and tolerable treatment option that is more effective and efficient than exposure-based psychotherapy monotherapy. This study represents the application of translational findings into a multisite clinical trial with the potential for shaping clinical practice for youth with OCD.

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