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RESEARCH ARTICLE

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Efficacy of D-cycloserine augmented brief intensive cognitive-behavioural therapy for paediatric obsessive-compulsive disorder: A randomised clinical trial

Lara J. Farrell[1] | Allison M. Waters[1] | Evelin Tiralongo[2] | Sharna Mathieu[1] | Matthew McKenzie[1] | Vinay Garbharran[1,3] | Robert S. Ware[4] | Melanie J. Zimmer-Gembeck[1,4] | Harry McConnell[4] | Cassie Lavell[5,6] | Jacinda Cadman[5] | Thomas H. Ollendick[7] | Jennifer L. Hudson[8] | Ronald M. Rapee[6] | Brett McDermott[9] | Daniel Geller[10] | Eric A. Storch[11]

[1]School of Applied Psychology, Griffith University, Gold Coast, Australia

[2]School of Pharmacy and Medical Sciences, Griffith University, Gold Coast, Australia

[3]Robina Private Hospital, Robina, Australia

[4]Menzies Health Institute Queensland, Griffith University, Gold Coast, Australia

[5]Children's Centre for Child Anxiety and OCD, Gold Coast, Australia

[6]Centre for Emotional Health, Macquarie University, Sydney, Australia

[7]Child Study Centre, Virginia Polytechnic University, Blacksburg, USA

[8]Black Dog Institute, University of New South Wales, Sydney, Australia

[9]James Cook University, Townsville, Australia

[10]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[11]Baylor College of Medicine, Houston, Texas, USA

Correspondence

Lara J. Farrell, School of Applied Psychology, Griffith University, Gold Coast Campus, QLD 4222, Australia.
Email: l.farrell@griffith.edu.au

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Abstract

Objective: To examine the efficacy of weight-adjusted D-cycloserine (DCS) (35 or 70 mg) relative to placebo augmentation of intensive exposure therapy for youth with obsessive-compulsive disorder (OCD) in a double-blind, randomised controlled trial, and examine whether antidepressant medication or patient age moderated outcomes.

Methods: Youth (n = 100, 7–17 years) with OCD were randomised in a 1:1 ratio to either DCS + exposure (n = 49) or placebo + exposure (n = 51). Assessments occurred posttreatment, 1 month later, and at 3 and 6 months. Pills were ingested immediately before sessions.

Results: Significant improvements on all outcomes were observed at posttreatment, and to 6-month follow-up. Treatment arms did not differ across time, with no significant time-by-medication interactions on symptom severity (T1 to T2 estimate: 9.3, 95% confidence interval [CI]: −11.2 to −7.4, and estimate −10.7, 95% CI: −12.6 to −8.7), diagnostic severity (T1 to T2 estimate: −2.0, 95% CI: −2.4 to −1.5 and estimate −2.5, 95% CI: −3.0 to −2.0) or global functioning (T1 to T2 estimate: 13.8, 95% CI: 10.6 to 17.0, and estimate 16.6, 95% CI: 13.2 to 19.9). Neither antidepressants at baseline nor age moderated primary outcomes. There were significantly fewer responders/remitters at 1- and 6-month follow-up among youth in the DCS condition stabilised on SSRIs, relative to youth not taking SSRIs.

Conclusions: DCS augmented intensive exposure therapy did not result in overall additional benefits relative to placebo. Intensive exposure proved effective in reducing symptoms for the overall sample.

KEYWORDS

cognitive-behaviour therapy, D-cycloserine, exposure therapy, OCD

1 | INTRODUCTION

Cognitive-behavioural therapy (CBT), involving exposure and response-prevention (ERP), either alone or in combination with antidepressant medication is the most widely endorsed, empirically-supported treatment for paediatric obsessive-compulsive disorder (OCD) (Geller et al., 2003; McGuire et al., 2015). Whilst highly effective, a significant proportion of those treated do not achieve remission following CBT highlighting a need for innovative approaches (McGuire et al., 2015). Novel and safe pharmacological approaches that augment the therapeutic effects of ERP may improve patient outcomes. *N*-methyl-D-aspartate partial agonist D-Cycloserine (DCS) has been shown in animals to facilitate the extinction of learned fear, the process hypothesized to underlie ERP, when ingested before or shortly after extinction training (Davis et al., 2006).

Clinical studies of DCS augmented ERP for OCD have however so far yielded inconsistent findings. In a preliminary randomised controlled trial (RCT), Farrell et al. (2013) reported significantly greater improvements in OCD symptoms for difficult-to-treat children and adolescents with OCD ($n = 17$) who received DCS augmented ERP relative to placebo (PBO) from posttreatment to 1-month follow-up. In contrast however, a large RCT ($n = 163$) of difficult-to-treat adults with OCD (Kvale et al., 2020) did not demonstrate overall benefits for DCS augmented intensive ERP (two doses over 2 consecutive days), despite earlier pilot RCTs with adults reporting significant benefits for DCS after only a few sessions of ERP (Kushner et al., 2007; Wilhelm et al., 2008). In a large RCT of youth, Storch et al. (2016) ($n = 142$) found no overall benefit for weight-adjusted DCS augmented CBT relative to placebo on OCD severity following 10 sessions of CBT, 7 of which were augmented with DCS/PBO. Similarly, Andersson et al. (2015) ($n = 128$) found no overall significant effects for DCS augmented internet delivered CBT relative to PBO in adults on OCD outcomes; however, DCS was associated with significantly higher remission rates in adults *not taking* antidepressants relative to patients on stable doses of antidepressants (60% vs. 24%). Notably, there were no differences in the PBO condition among patients taking antidepressant or not taking antidepressants (50% both groups). The moderating effects of antidepressant use on DCS augmentation, suggests anti-depressant use may block the facilitating effects of DCS on exposure outcomes. In a large individual patient data meta-analysis, Mataix-Cols et al., (2017) found overall small augmentation effects for DCS relative to placebo at posttreatment ($n = 1047$ of 21 studies); however, in subgroup analyses found no superiority of DCS for OCD patients, and moreover, failed to replicate the moderating effects of antidepressant medication previously reported by Andersson et al. (2015). The inconsistent findings of DCS outcomes across trials to date, suggest that positive augmentation of DCS may be associated with specific clinical/patient and/or dosing parameters, which require further investigation given the safety, tolerability and promise of DCS in improving patients' outcomes (Mataix-Cols et al., 2017).

In other efforts to enhance exposure outcomes, recent experimental psychotherapy research highlights the importance of enhancing engagement and arousal *during* exposure therapy to maximise extinction learning and exposure therapy outcomes (Craske et al., 2014; Waters & Craske, 2016). Enhancing variability during exposure trials has been argued to enhance engagement in several ways, including making the learning task more salient and memorable (Bjork & Bjork, 2006), and linking new learning with greater retrieval cues (Estes, 1955). Including multiple stimuli representative of the feared stimulus during extinction has been found to increase physiological arousal during extinction yet enhance generalization of extinction learning to novel stimuli and prevent return of fear compared to the conditioned stimuli alone (Hermans et al., 2006; Rowe & Craske, 1998; Waters et al., 2018; Waters et al., 2021). Furthermore, conducting exposure trials across multiple different contexts (e.g., therapist office; public bathroom; local shopping centre) also enhances extinction learning and prevents relapse (Balooch et al., 2012; Vansteenwegen et al., 2007). Notably, a recent study found that combining *prolonged* extinction training with extinction delivered across multiple contexts, resulted in greater cross-contextual generalizability and reduction of renewal of fear relative to either prolonged extinction training alone, or extinction in multiple contexts alone (Krisch et al., 2018). The authors of that study propose that prolonged exposure therapy sessions, in addition to exposure delivered across multiple contexts, may result in greater fear reduction and prevent relapse.

Given early evidence suggesting DCS effects occur early in treatment after only a few sessions (Kushner et al., 2007; Wilhelm et al., 2008), combined with evidence for *enhanced* ERP outcomes when ERP is delivered across multiple contexts (Waters et al., 2018; Weisman & Rodebaugh, 2018) in combination with trials (Krisch et al., 2018), the efficacy of DCS augmented brief, *intensive* ERP *across multiple contexts* for paediatric OCD extends existing literature. The current study is a PBO-controlled, double-blind RCT of DCS augmented intensive ERP for paediatric OCD, consisting of three weekly 3-h sessions, and a 1-month booster session, with sessions conducted across settings. The primary aim was to compare weight-adjusted (35 mg/70 mg) (Farrell et al., 2013; Storch et al., 2016; Storch, Murphy, et al., 2010) DCS augmented intensive ERP (ERP + DCS) relative to intensive ERP and placebo (ERP + PBO) among youth (7–17 years) with a primary diagnosis of OCD and evaluate outcomes at posttreatment (T2), 1-month (T3), 3-month (T4), and 6-month (T5) follow-up. Primary end point was 1 month following baseline at completion of treatment; however, all time points were examined in analytic models given evidence for augmentation effects at mid-treatment, and importance of longer-term outcomes. It was hypothesised that patients receiving ERP + DCS would demonstrate significantly greater improvements relative to ERP + PBO at all time points on primary (symptom severity (Scahill et al., 1997), diagnostic severity (Silverman, 1996), functioning (Shaffer et al., 1983), and secondary (parent/child rated target symptoms and OCD-impairment) outcome measures, and achieve better treatment response and remission.

Potential moderating effects of child age and antidepressant medication status were explored, given past studies suggesting stronger augmenting effects among younger phobic children (<11 years), relative to older adolescents (>12 years) (Farrell et al., 2018), and for patients *not taking* antidepressant medication relative to those on stable doses (Andersson et al., 2015). It was hypothesized that the benefits of DCS would be stronger for younger children (7–11 years), and those not on antidepressant medication across all outcome measures.

2 | METHODS

2.1 | Participants

This RCT was conducted at Griffith University, Australia (2015–2019) a specialist OCD research and treatment clinic for children and adolescents. Children (7–17 years) were screened for inclusion and eligible if: (1) (co)primary diagnosis of at least moderately severe OCD (i.e., ≥16 on the CY-BOCS, Scahill et al., 1997); and (2) a stable dose of antipsychotic or antidepressant medication before enrolling, where applicable (i.e., 12-week postinitiation or 6-week postdosage change), and willingness to maintain a stable dose for the duration. Exclusion criteria included: (1) receiving concurrent psychological treatment, (2) comorbid psychosis, bipolar disorder, eating disorder and/or autism-spectrum disorder level two or three, (3) active suicidality, (4) poor physical health (e.g., low weight, renal failure, heart condition, epilepsy), (5) pregnant or possibility of becoming pregnant, (6) unable/unwilling to have a blood test or swallow study medication. Appropriate referrals were provided to all excluded participants. Children who met inclusion underwent double-blind randomisation to either weight-adjusted ERP + DCS (35 mg or 75 mg) or ERP + a placebo tablet (Figure 1).

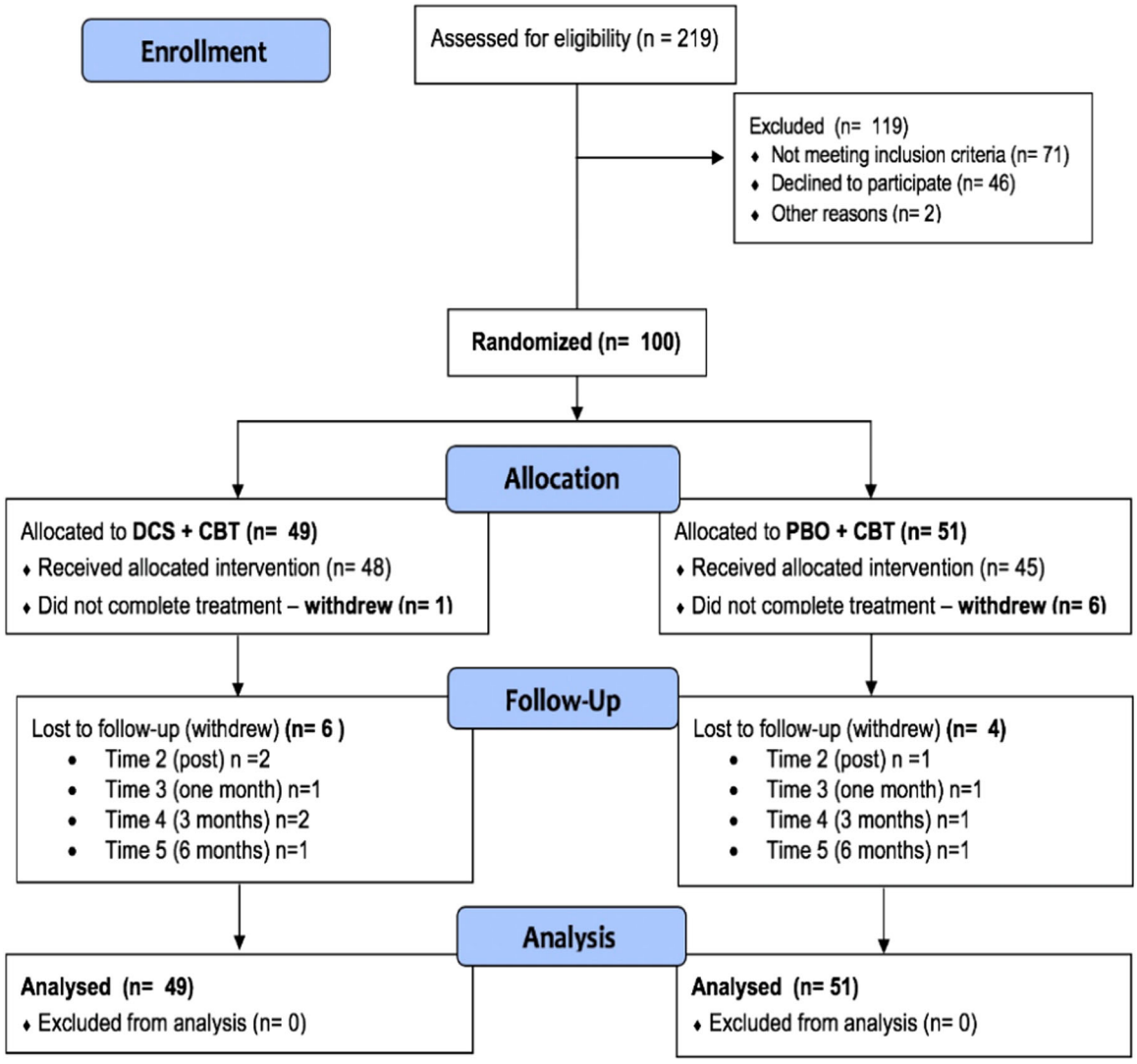

FIGURE 1 Participant consort flow diagram

2.2 | Measures

2.2.1 | Anxiety Disorders Interview Schedule–Parent (ADIS-P)

The ADIS-P CSR was the primary outcome for OCD diagnostic severity (Silverman, 1996). The CSR ranges from 0 to 8, with 4 and above indicating diagnosis. All interviews underwent consensus supervision (LJF) to resolve discrepancies and moderate ratings. Further, all primary diagnoses were verified independently by a child psychiatrist (VG) who prescribed the study medications (100% consensus). Finally, a masked independent rater reviewed a random sample of recorded interviews (16%) to determine inter-rater reliability of the primary diagnosis, which was excellent (kappa = 1.00) (Silverman, 1996).

2.3 | Primary outcomes

2.3.1 | Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)

The CY-BOCS is comprised of two symptoms checklists (obsessions and compulsions) and five subscales (time, distress, interference, resistance, control) that indicate Obsessions severity, Compulsion severity and Total Severity (Scahill et al., 1997). It is administered in a semi-structured interview format, and was completed face-to-face at baseline, and via the telephone with the parent and child on speaker for every other assessment point.

2.3.2 | Children's Global Assessment Scale (CGAS)

The CGAS provides a single score of a child's global functioning (1 = poorest functioning to 100 = highest functioning) and captures important clinical information beyond diagnostic categories (Shaffer et al., 1983). Functioning was reviewed during assessment supervision with the lead author (LJF) and determined based upon the overall assessment results of the ADIS-P, CY-BOCS and clinical impression.

2.4 | Secondary outcomes

2.4.1 | Child Obsessive-Compulsive Impact Scale–Parent Rated (COIS-P)

The COIS-P is a parent rated self-report measures widely used to assess perceptions of OCD-related impairment (school, social, home, global) (Piacentini & Jaffer, 1999). The measure contains 56 items and has demonstrated excellent psychometric properties.

2.4.2 | Target symptoms–parent/child rated

Three individualised target obsessions (TS obsessions) and three target compulsions (TS compulsions) were obtained for each child, which represented symptoms of highest clinical significance. Target symptoms were rated by the child and parent/s indicating the child's level of distress/difficulty associated with each symptom (e.g., obsession of harm coming to parents; compulsion of lengthy bedtime ritual) on a scale ranging from 0 to 8 (*how fearful/difficult?* 0 = none to 8 = very much). Target symptom ratings were averaged across the three symptoms to provide a mean target symptom obsession and target symptom compulsion score (Farrell et al., 2018; Oar et al., 2015).

2.4.3 | Adverse Schedule Checklist (ASC)

To monitor potential medication-related adverse effects, parents and children were administered an ASC (Farrell et al., 2013; Storch et al., 2010) in line with previous studies. The ASC is a 30-item checklist that screens for common side effects of medication (e.g., headaches, constipation, blurred vision, dry mouth). Children (with parents present) rated symptoms over the past week on a Likert scale from 0 "*not at all*" to 3 "*severe*." 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.

2.4.4 | Treatment satisfaction–parent/child rated

Parents and children completed a satisfaction measure upon completion of the therapy, which was developed for the purpose of this trial. The brief measure assessed how acceptable and helpful the treatment was (i.e., overall, my treatment was helpful to me; since completing the treatment my child is better able to cope with his/her OCD) on a 5-point Likert scale. There were 4 items for children (score range: 4–20) and 7 items for parents (range: 7–35) with higher scores indicating higher treatment satisfaction.

2.5 | Procedure

Ethical approval was provided by the institution's human research ethics committee (Ref no. PSY/D8/14/HREC). Written informed consent was provided by all parents and children. The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000473460).

2.5.1 | Baseline (eligibility) assessment

Before randomisation, parents completed an initial telephone screen before proceeding to a full diagnostic interview where the ADIS-P was administered to parents over the telephone by trained clinicians/researchers. Upon receiving a primary diagnosis of OCD, the CY-BOCS was completed with parent/child face-to-face with their treating clinician, and a full medical review was provided by a child psychiatrist (VG). Participants who met inclusion criteria were randomized and received either ERP + DCS or ERP + PBO (1:1). Randomisation occurred in a 1:1 ratio and all authors (except ET), treating clinicians, and participants were masked to condition. An online randomization program (randomization.com) generated the double-blind lists.

2.5.2 | Intervention and evaluation

Participants received face-to-face intensive ERP treatment, following a brief psychoeducation session which occurred following the CY-BOCS interview at baseline. The following three weekly ERP sessions were 3.0–3.5 h in duration (with at least one session conducted at home). The final treatment session was a 1-month booster session focusing on ERP and relapse prevention (1.5–2.0 h).

Immediately before each ERP session the child ingested the tablet (PBO or weight-adjusted dose of 35 mg or 70 mg DCS). Capsules were dispensed via the study pharmacist (ET). All treatment was provided by trained and registered psychologists receiving ongoing weekly supervision from the lead author (LJF). The intensive ERP treatment approach is described elsewhere in detail (Dayson et al., 2019; Farrell et al., 2016).

All posttreatment ADIS-P and CY-BOCS interviews were conducted by trained research assistants masked to study randomisation. All posttreatment primary and secondary assessments were completed via the telephone, expect for the parent-rated measure the COIS-P, which was completed by parents via an online survey at 1-month follow-up only.

2.6 | Study power and analytic plan

The a prior planned sample size calculation ($n = 116$) was determined to detect a small treatment condition × time interaction ($F = 0.11$) and a medium treatment condition (ERP + DCS vs. ERP + PBO) difference ($d = 0.55$) at any single time point, with 80% power at $\alpha = .05$, which allowed for 10% attrition (final proposed sample, $n = 106$). Study recruitment and enrolment was slower than anticipated and as such the final sample was below target ($n = 100$, power 77% to detect mean difference [MD] $d = 0.55$, $\alpha = .05$).

Primary and secondary treatment outcomes were analysed using linear mixed-effects models with treatment condition and time as main effects, and a condition × time interaction, using an intention to treat approach. Participant was specified as a random effect to account for the repeated-measures nature of the data. Missing data was not imputed. To examine between condition differences in treatment response and remission, χ^2-analyses were used. "Response" was a reduction of ≥35% on CY-BOCS severity, whereas "remission" was a posttreatment or follow-up CY-BOCS of ≤12 (Farhat et al., 2021).

To test moderating effects of concomitant antidepressant medication and child age on outcomes separately, linear mixed models were estimated specifying antidepressant status (no/yes) and age (7–11 years/12–17 years) as dichotomous fixed factors, and testing 3-way interactions of treatment condition × time × antidepressant medication status, and treatment condition × time × child age (7–11 vs. 12–17 years). As post hoc analyses, models were re- run after stratification for current SSRI use and child age. Data analysis was undertaken using Stata statistical software v14 (StataCorp).

3 | RESULTS

3.1 | Sample characteristics

Participant flow through the RCT is displayed in Figure 1. Two hundred and nineteen participants were screened for eligibility. Of these, 100 participants met eligibility and were enrolled/randomised. Seven participants withdrew after allocation to treatment, including one from ERP + DCS, and six from ERP + PBO. Reasons were difficulty with scheduling appointments ($n = 4$), child refusal to engage in therapy ($n = 1$), and child inability to swallow study medication ($n = 2$). Figure 1 illustrates loss of participants from the trial over time. Missing data on primary outcomes at follow-up assessment points occurred typically due to participants being too busy to complete the assessment at that point in time, and increased across follow-up from 10% at Time 2, to 21% across Time 3 and 4, and 26% at Time 5.

Table 1 presents baseline sample characteristics by treatment condition. Baseline values of outcome variables are presented in Table 2.

3.2 | Primary analyses (DCS vs. Placebo)

Preliminary analyses revealed significant improvements on all outcomes from T1 to T2 for both treatment groups, followed by lesser change from T2 to T5; thus, models were fit to summarise improvement from T1 to T2 separate from T2 to T5 changes. Table 2 displays between-condition comparisons at each time point. Parameter estimates derived from regression models from Time 1 to Time 2 are detailed in Table 3, while estimates from Time 2 to Time 5 are detailed in Table 4. Although all outcomes improved significantly over time, there were no statistically significant between-comparison effects at any time point on any study outcome variable (Table 2). Similarly, there were no significant timeXtreatment interaction effects on primary outcomes. For example, although large improvements were observed on CY-BOCS total severity for both the DCS

TABLE 1 Baseline demographic and clinical characteristics

Sample characteristic	PBO (*N* = 51)	DCS (*N* = 49)	*p* value
Age, mean (*SD*)	11.7 (2.5)	12.3 (2.4)	.23
Female, *n* (%)	25 (49.0%)	28 (57.1%)	.42
Stable antidepressant, *n* (%)	21 (41.2%)	16 (32.7%)	.52
Number comorbidities, mean (*SD*)	1.9 (1.6)	1.6 (1.4)	.24
Number comorbidities, *n* (%)			.88
OCD only	10 (19.6%)	12 (24.5%)	
OCD and 1 additional	14 (27.5%)	15 (30.1%)	
OCD and 2 additional	13 (25.5)	12 (24.5%)	
OCD and 3 or more	14 (27.4%)	10 (20.9%)	

Note: *n* (%) = number (percentage); Stable Antidepressant includes any serotonin reuptake inhibitors or tricyclic antidepressant medication.
Abbreviation: *SD*, standard deviation.

and PBO conditions from pre- to posttreatment (DCS [MD]; 95% confidence interval) = −9.3; −11.2 to −7.4; PBO = −10.7; −12.6 to −8.7), the difference between conditions posttreatment was non-significant (MD = 1.2; −1.7 to 2.7). The statistically significant improvements at posttreatment (T2) on all measures were maintained across all time points (T3–T5) for both conditions (Table 5).

3.3 | Responder and remission status across groups

Response and remission rates did not differ significantly between treatment conditions (see Table 6, all $p > .05$). At posttreatment (T2), 47% (DCS) and 58% (PBO) of patients were "responders," which improved to 69% for those in the DCS condition and 74% for PBO at 6-month follow-up. In terms of "remission," 21% (DCS) and 28% (PBO) of patients remitted at Time 2, with remission at 6 months increasing to 49% (DCS) and 51% (PBO).

3.4 | Moderating effects of current antidepressants and child age on outcomes

Three-way interaction effects were not significant for any primary or secondary outcome variables (all $p > 0.05$) suggesting neither concurrent antidepressant medication use or child age moderated treatment outcomes. To examine the size of treatment effects of SSRI use and age, stratified analyses were conducted.

3.5 | Subgroup analyses

There were improvements on all outcomes for both antidepressant medication sub-groups, but there were no effects of treatment condition and no time × condition effects. In subgroup analyses of age, there were improvements on all outcomes for both age groups but there were no effects for treatment condition and no time × condition effects.[1]

Among youth who were randomised to ERP + DCS there were significantly fewer responders at Time 3, $\chi^2(1, 42) = 4.20$, $p = .04$, $\phi = -.35$ for youth taking SSRI medication (43%) relative to youth not taking SSRI medication (75%). There were also significantly fewer remitters at Time 3, $\chi^2(1, 42) = 5.97$, $p = .01$, $\phi = -.35$ for youth taking SSRI medication (14%) relative to youth not taking SSRI medication (54%). Similarly, at Time 5 there were significantly fewer responders $\chi^2(1, 39) = 7.13$, $p = .008$, $\phi = -.35$ among youth taking SSRI medication (43%) relative to youth not taking SSRI medication (84%), as well as a trend towards fewer remitters among youth taking SSRI medication (29%) relative to those not taking SSRI medication (60%), $p = .06$.

3.6 | Adverse events and treatment satisfaction

Condition was not associated with frequency of adverse effects (mean [*SD*] for ERP + DCS = 4.8 [10.7] vs. ERP + PBO = 3.1 [5.5]; $p > .05$). Overall, children and parents rated treatment as highly acceptable. For children, mean satisfaction ratings were 17.7 (*SD* = 3.0; range: 4–20) and for parents 32.8 (*SD* = 3.1; range: 7–35).

4 | DISCUSSION

This study is the first double-blind RCT of DCS augmented *intensive* CBT for children and adolescents with OCD and extends the literature by (a) enhancing the quality of ERP via intensive sessions, delivered across contexts; (b) examining incremental effects of DCS across time, including after a booster session/dose at 1-month follow-up; (c) examining longer-term outcomes to 6-month follow-up; and (d) examining the potential moderating effects of antidepressant use. Overall, we found no evidence for augmenting effects of DCS at posttreatment, or at any follow-up point. In particular, and in contrast to previous RCTs, we found no evidence for accelerated improvement associated with DCS augmentation from post to 1-month follow-up (Chasson et al., 2010; Farrell et al., 2013). We also found no moderating effects of SSRI medication or age associated with DCS outcomes on primary and secondary measures for the overall sample. In sub-group analyses, there were significantly fewer responders and remitters within the DCS condition among youth taking SSRI medication, relative to youth not on SSRI medication.

The findings reported here are consistent with the only other large RCT of DCS augmented CBT for youth with OCD (Storch et al., 2016), which found no overall benefits for DCS, or moderating effects of

[1]Parameter estimates for all sub-group analyses are available as Tables (S1–S4).

TABLE 2 Summary statistics for primary and secondary outcomes, and mean treatment group differences at each time of measurement

Outcome variable	PBO (*N* = 51) mean (*SD*)	DCS (*N* = 49) mean (*SD*)	Mean difference (95% CI)	*p* value
Primary outcomes				
Total CY-BOCS				
Pretreatment	27.4 (3.9)	27.2 (4.2)	−0.2 (−3.0, 2.7)	
Posttreatment	16.4 (6.8)	17.9 (6.1)	1.2 (−1.7, 4.2)	.42
1 month	13.6 (9.2)	15.0 (8.8)	1.2 (−1.9, 4.3)	.44
3 months	14.0 (8.9)	14.6 (8.6)	0.7 (−2.4, 3.7)	.66
6 months	12.9 (9.7)	13.2 (8.1)	0.3 (−2.8, 3.5)	.84
Clinician severity rating (CSR)				
Pretreatment	6.5 (0.8)	6.2 (1.0)	−0.2 (−0.9, 0.4)	
Posttreatment	3.9 (1.6)	4.3 (1.5)	0.3 (−0.4, 1.0)	.35
1 month	3.2 (2.1)	3.5 (2.0)	0.3 (−0.4, 1.0)	.42
3 months	3.4 (2.0)	3.3 (2.0)	−0.1 (−0.8, 0.6)	.75
6 months	2.9 (2.2)	3.1 (2.0)	0.2 (−0.5, 0.9)	.75
Global functioning (CGAS)				
Pretreatment	52.0 (7.0)	53.7 (6.6)	1.5 (−2.6, 5.6)	
Posttreatment	n/r	n/r	n/r	n/r
1 month	69.2 (11.0)	67.8 (13.0)	−1.2 (−5.6, 3.2)	.60
3 months	68.9 (10.5)	68.2 (12.2)	−0.3 (−4.8, 4.2)	.90
6 months	67.4 (13.9)	69.6 (10.8)	0.9 (−3.7, 5.6)	.69
Secondary outcomes				
Target obsessions rating—child				
Pretreatment	5 (1.6)	4.7 (1.7)	−0.3 (−0.9, 0.42)	
Posttreatment	2.8 (2)	3.1 (1.7)	0.3 (−0.4, 1.0)	.48
1 month	2.2 (2)	2.1 (1.8)	−0.2 (−0.9, 0.6)	.64
3 months	2.2 (1.9)	2 (1.7)	−0.2 (−1.0, 0.5)	.54
6 months	1.8 (2.1)	1.7 (1.5)	0.2 (−0.9, 0.6)	.66
Target obsessions rating—parent				
Pretreatment	5.5 (1.5)	4.8 (1.5)	−0.6 (−1.3, 0.1)	
Posttreatment	2.8 (1.9)	3.4 (1.8)	0.4 (−0.2, 1.1)	.23
1 month	2.6 (2)	2 (1.9)	−0.2 (−1.0, 0.5)	.50
3 months	2.4 (1.9)	2.4 (2.1)	0.04 (−0.7, 0.8)	.91
6 months	1.9 (2)	1.7 (1.8)	−0.2 (−1.0, 0.5)	.56
Target compulsions rating—child				
Pretreatment	5.6 (1.4)	5.4 (1.6)	−0.2 (−0.9, 0.4)	
Posttreatment	2.5 (1.9)	3.3 (1.8)	0.7 (0.01, 1.5)	.04
1month	1.7 (1.6)	2.1 (1.9)	0.3 (−0.5, 1.0)	.49
3 months	2.1 (1.9)	2.3 (1.9)	0.1 (−0.6, 0.9)	.72
6 months	1.7 (1.7)	1.7 (1.5)	0.1 (−0.7, 0.8)	.82

(Continues)

TABLE 2 (Continued)

Outcome variable	PBO (*N* = 51) mean (*SD*)	DCS (*N* = 49) mean (*SD*)	Mean difference (95% CI)	*p* value
Target compulsions rating—parent				
Pretreatment	5.9 (1.3)	5.2 (1.5)	−0.6 (−1.3, 0.1)	
Posttreatment	2.6 (1.8)	3.3 (1.9)	0.6 (−0.1, 1.3)	.08
1 month	2.3 (2.1)	2 (1.6)	−0.2 (−0.9, 0.5)	.65
3 months	1.9 (1.8)	2.1 (1.8)	0.1 (−0.6, 0.9)	.71
6 months	1.9 (2.3)	1.6 (1.8)	−0.3 (−1.1, 0.4)	.36
Child OCD impairment—parent (COIS-P)				
Pretreatment	49.3 (29.3)	39.2 (26.5)	−10.2 (−20.7, 0.2);	
1 month	24.7 (23.9)	19.2 (21.6)	−6.2 (−17.6, 5.2);	.29

Abbreviations: CI, confidence interval; DCS, D-cycloserine.

TABLE 3 Parameter estimates for outcomes across time (Time 1 to Time 2) and between treatment conditions (*N* = 100)

Effect	Outcome variables, *B* (*SE*)					
	CYBOC-Total	CSR	Target O_C	Target O_P	Target C_C	Target C_P
Condition (ERP + DCS vs. ERP + PBO)	−0.1 (1.1)	−0.2 (0.2)	−0.3 (0.3)	−0.7 (0.3)	−0.2 (0.3)	−0.7 (0.3)
Time (pre- to posttreatment)	−11.0 (0.9)***	−2.6 (0.2)***	−2.2 (0.3)***	−2.6 (0.3)***	−3.1 (0.3)***	−3.4 (0.3)***
Condition × Time	1.7 (1.2)	0.6 (0.3)	0.6 (0.5)	1.2 (0.4)**	1.1 (0.5)*	1.4 (0.4)**
Stratified by antidepressant status: no current SSRI use (*n* = 63)						
Condition ERP + PBO vs. ERP + DCS)	0.1 (1.4)	−0.2 (0.3)	−0.5 (0.4)	−0.6 (0.4)	−0.3 (0.5)	−0.6 (0.4)
Time	−10.3 (1.1)	−2.5 (0.3)	−2.5 (0.4)	−2.8 (0.4)	−3.1 (0.4)	−3.2 (0.4)
Condition × Time	0.7 (1.5)	0.3 (0.4)	0.8 (0.5)	1.1 (0.5)*	0.9 (0.6)	1.2 (0.5)*
Stratified by antidepressant status: current SSRI use (*n* = 37)						
Condition	−0.3 (1.6)	−0.2 (0.4)	0.0 (0.6)	−0.7 (0.6)	−0.1 (0.5)	−0.8 (0.5)
Time	−12.2 (1.4)	−2.7 (0.4)	−1.7 (0.6)	−2.4 (0.5)	−3.2 (0.5)	−3.6 (0.4)
Condition × Time	3.4 (2.1)	1.1 (0.5)*	0.2 (0.8)	1.4 (0.7)*	1.3 (0.7)	1.8 (0.6)**
Stratified by age: 7–11 years (*n* = 38)						
Condition	−0.3 (1.9)	−0.2 (0.4)	0.0 (0.6)	−0.5 (0.6)	−0.8 (0.6)	−1.2 (0.6)
Time	−11.7 (1.3)	−2.4 (0.3)	−2.0 (0.5)	−2.1 (0.4)	−3.2 (0.5)	−3.3 (0.4)
Condition × Time	1.9 (2.1)	0.4 (0.5)	0.2 (0.9)	0.6 (0.7)	1.9 (0.8)*	2.1 (0.7)**
Stratified by age: 12–17 years (*n* = 62)						
Condition	−0.3 (1.3)	−0.3 (0.3)	−0.5 (0.4)	−1.0 (0.4)	0.0 (0.4)	−0.5 (0.4)
Time	−10.3 (1.2)	−2.7 (0.3)	−2.4 (0.4)	−3.2 (0.4)	−3.1 (0.4)	−3.4 (0.4)
Condition × Time	1.3 (1.5)	0.8 (0.4)	0.9 (0.6)	1.7 (0.5)***	0.7 (0.5)	1.1 (0.05)*

Note: The "Condition" coefficient represents the mean difference between treatment condition. The 'Time' coefficient represents change (increase or decrease if negative) in outcome from pre- to posttreatment. The interaction term is the between-group difference in pre- to posttreatment change. CSR = clinician severity rating; Target O_C = target obsession rating child; Target O_C = target obsession rating parent; Target C_C = target compulsion rating child; Target C_P = target compulsion rating parent. SSRI = selective serotonin reuptake inhibitor. Significance: *$p < .05$; **$p < .005$; ***$p < .001$.

Abbreviations: DCS, D-cycloserine; ERP, exposure and response-prevention.

TABLE 4 Parameter estimates for outcomes across Time (Time 2 to Time 5) and treatment condition ($N = 100$)

Effect	Outcome variables, B (*SE*)						
	CSR	CGAS	CYBOC-Total	Target O_C	Target O_P	Target C_C	Target C_P
Condition (ERP + DCS vs. ERP + PBO)	0.38 (0.35)	−2.22 (2.55)	1.31 (1.48)	0.13 (0.37)	0.52 (0.35)	0.58 (0.37)	0.63 (0.38)
Time (T2 to T5)	−0.11 (0.04)**	−0.21 (0.34)	−0.37 (0.16)*	−0.14 (0.04)***	−0.13 (0.04)***	−0.08 (0.04)	−0.08 (0.04)
Condition × Time	−0.03 (0.06)	0.40 (0.47)	−0.18 (0.22)	−0.04 (0.06)	−0.08 (0.06)	−0.08 (0.06)	−0.12 (0.06)
Stratified by antidepressant status: no current SSRI use ($n = 63$)							
Condition	0.09 (0.43))	−2.88 (3.22)	0.42 (1.73)	0.25 (0.45)	0.38 (0.43)	0.54 (0.48)	0.58 (0.46)
Time (months)	−0.14 (0.05)**	−0.41 (0.42)	−0.53 (0.21)*	−0.10 (0.05)*	−0.15 (0.05)**	−0.08 (0.05)	−0.14 (0.05)**
Condition × Time	−0.03 (0.07)	0.75 (0.56)	−0.14 (0.28)	−0.05 (0.07)	−0.06 (0.07)	−0.08 (0.07)	−0.08 (0.07)
Stratified by antidepressant status: current SSRI use ($n = 37$)							
Condition	0.97 (0.54)	−2.66 (3.97)	3.17 (2.54)	0.20 (0.60)	0.82 (0.57)	0.69 (0.54)	0.71 (0.65)
Time (months)	−0.06 (0.06)	0.10 (0.59)	−0.13 (0.25)	−0.20 (0.07)**	−0.10 (0.07)	−0.07 (0.07)	0.03 (0.07)
Condition × Time	−0.03 (0.09)	−0.26 (0.85)	−0.20 (0.35)	−0.02 (0.09)	−0.11 (0.09)	−0.08 (0.10)	−0.20 (0.09)*
Stratified by age: 7–11 years ($n = 38$)							
Condition	0.22 (0.50)	2.17 (4.02)	1.90 (2.30)	0.45 (0.64)	0.37 (0.53)	0.83 (0.56)	1.00 (0.61)
Time (months)	−0.13 (0.06)*	0.03 (0.38)	−0.33 (0.23)	−0.09 (0.05)	−0.21 (0.05)***	−0.12 (0.06)	−0.16 (0.05)**
Condition × Time	−0.02 (0.09)	−0.28 (0.62)	−0.06 (0.38)	−0.20 (0.08)*	−0.03 (0.08)	−0.12 (0.10)*	−0.10 (0.09)
Stratified by age: 12–17 years ($n = 62$)							
Condition	0.39 (0.47)	−4.26 (3.36)	0.37 (1.94)	−0.17 (0.46)	0.62 (0.48)	0.30 (0.49)	0.37 (0.49)
Time (months)	−0.08 (0.06)	−0.56 (0.58)	−0.40 (0.23)	−0.19 (0.06)**	−0.03 (0.06)	−0.01 (0.06)	0.03 (0.06)
Condition × Time	−0.06 (0.08)	0.95 (0.72)	−0.22 (0.28)	0.06 (0.07)	−0.16 (0.08)*	−0.11 (0.08)	−0.21 (0.07)**

Note: The "Condition" coefficient represents the mean difference between treatment condition. The "Time" coefficient represents change (increase or decrease if negative) in outcome from T2 to T5. The interaction term is the between-condition difference in change from T2 to T5. Significance: *$p < .05$; **$p < .005$; ***$p < .001$.

Abbreviations: DCS, D-cycloserine; ERP, exposure and response-prevention.

antidepressant medications. Our findings are also consistent with Kvale et al. (2020) in their RCT of intensively delivered ERP among adults with OCD. Collectively, results suggest that DCS does not augment ERP whether delivered across multiple weekly sessions (Storch et al., 2016), or across concentrated daily sessions (Kvale et al., 2020), or when delivered in a brief, weekly format. We did however find attenuated response and remission rates to ERP among youth in the ERP + DCS condition who were stabilised on antidepressant medication, relative to youth not on SSRIs, a pattern which was not observed in the ERP + PBO condition. This finding is consistent with those reported by Andersson et al. (2015) in their RCT of DCS augmented ERP for adults with OCD, which concluded that antidepressant medication may block the facilitating effects of DCS on exposure outcomes. However, in the Andersson et al., (2015) trial, antidepressant use was also found to be a significant moderator of primary and secondary outcomes in the mixed-linear models. Given the relatively small cell sizes in sub-group analyses of responders and remitters across conditions in the current study, the findings reported here should be interpreted with caution. Further research with larger samples, and with antidepressant naïve youth, are necessary to determine the small effect sizes associated with DCS augmentation.

The current trial provides further evidence for the effectiveness of brief and intensive ERP, delivered across the home and clinic for paediatric OCD. Response and remission rates reported in this trial are consistent with those found in trials of routinely delivered weekly CBT, typically delivered over 3 months or more (>12 weekly sessions). We found response rates between 47% and 58% at posttreatment after only *3 weeks* of ERP (and 64% and 72% at Time 3, which coincides with the completion of treatment), with further improvement by 6-month follow-up (69%–74% response). Remission rates at posttreatment were between 21% and 28% (and 41%–51% at time 3 following the booster session) and improved further to between 49% and 51% at 6-month follow-up. These outcomes largely parallel meta-analytic results with mean response rates of 68% and remission rates of 57% at posttreatment (McGuire et al., 2015). Given the highly debilitating and disruptive nature of OCD to a child's life, evidence for a more concentrated, efficient mode of therapy is likely to be appealing to families and clinicians alike. Indeed, both parents and children in the current trial reported high acceptability and satisfaction with this treatment. Of note, given that approximately 30% of youth with OCD did not achieve a clinical response to intensive ERP, and furthermore, approximately 50% did not remit, further research aimed at examining optimal "dose" of ERP for non-responders and partial-

TABLE 5 Summary statistics for primary and secondary outcomes, and the association within-treatment for outcome variables

Outcome variable	PBO (*N* = 51) mean (*SD*)	Mean difference (95% CI)	*p* value	DCS (*N* = 49) mean (*SD*)	Mean difference (95% CI)	*p* value
Primary outcomes						
Total CY-BOCS						
Pretreatment	27.4 (3.9)	Ref.	Ref.	27.2 (4.2)	Ref.	Ref.
Posttreatment	16.4 (6.8)	−10.7 (−12.6, −8.7)	<.001	17.9 (6.1)	−9.3 (−11.2, −7.4)	<.001
1 month	13.6 (9.2)	−13.8 (−15.8, −11.7)	<.001	15.0 (8.8)	−12.4 (−14.4, −10.4)	<.001
3 months	14.0 (8.9)	−13.4 (−15.4, −11.4)	<.001	14.6 (8.6)	−12.6 (−14.6, −10.6)	<.001
6 months	12.9 (9.7)	−13.9 (−15.4, −11.4)	<.001	13.2 (8.1)	−13.4 (−15.5, −11.4)	<.001
Clinician severity rating (CSR)						
Pretreatment	6.5 (0.8)	Ref.	Ref.	6.2 (1.0)	Ref.	Ref.
Posttreatment	3.9 (1.6)	−2.5 (−3.0, −2.0)	<.001	4.3 (1.5)	−2.0 (−2.4, −1.5)	<.001
1 month	3.2 (2.1)	−3.3 (−3.8, −2.8)	<.001	3.5 (2.0)	−2.8 (−3.2, −2.3)	<.001
3 months	3.4 (2.0)	−3.0 (−3.5, −2.5)	<.001	3.3 (2.0)	−2.9 (−3.4, −2.4)	<.001
6 months	2.9 (2.2)	−3.4 (−3.9, −2.9)	<.001	3.1 (2.0)	−3.0 (−3.5, −2.5)	<.001
Global functioning (CGAS)						
Pretreatment	52.0 (7.0)	Ref.	Ref.	53.7 (6.6)	Ref.	Ref.
1 month	69.2 (11.0)	16.6 (13.2, 19.9)	<.001	67.8 (13.0)	13.8 (10.6, 17.1)	<.001
3 months	68.9 (10.5)	16.3 (12.9, 19.7)	<.001	68.2 (12.2)	14.5 (11.3, 17.7)	<.001
6 months	67.4 (13.9)	15.6 (12.1, 19.1)	<.001	69.6 (10.8)	15.0 (11.7, 18.3)	<.001
Secondary outcomes						
Target obsessions rating—child						
Pretreatment	5 (1.6)	Ref.	Ref.	4.7 (1.7)	Ref.	Ref.
Posttreatment	2.8 (2)	−2.1 (−2.7, −1.6)	<.001	3.1 (1.7)	−1.6 (−2.1, −1.0)	<.001
1 month	2.2 (2)	−2.7 (−3.3, −2.2)	<.001	2.1 (1.8)	−2.7 (−3.2, −2.1)	<.001
3 months	2.2 (1.9)	−2.8 (−3.4, −2.2)	<.001	2 (1.7)	−2.8 (−3.3, −2.2)	<.001
6 months	1.8 (2.1)	−3.1 (−3.7, −2.5)	<.001	1.7 (1.5)	−3.0 (−3.6, −2.5)	<.001
Target obsessions rating—parent						
Pretreatment	5.5 (1.5)	Ref.	Ref.	4.8 (1.5)	Ref.	Ref.
Posttreatment	2.8 (1.9)	−2.5 (−3.0, −2.0)	<.001	3.4 (1.8)	−1.4 (−1.9, −1.0)	<.001
1 month	2.6 (2)	−3.0 (−3.5, −2.4)	<.001	2 (1.9)	−2.6 (−3.1, −2.1)	<.001
3 months	2.4 (1.9)	−3.1 (−3.6, −2.6)	<.001	2.4 (2.1)	−2.4 (−2.9, −1.9)	<.001
6 months	1.9 (2)	−3.4 (−4.0, −2.9)	<.001	1.7 (1.8)	−3.0 (−3.5, −2.5)	<.001
Target compulsions rating—child						
Pretreatment	5.6 (1.4)	Ref.	Ref.	5.4 (1.6)	Ref.	Ref.
Posttreatment	2.5 (1.9)	−3.1 (−3.6, −2.5)	<.001	3.3(1.8)	−2.1 (−2.6, −1.5)	<.001
1 month	1.7 (1.6)	−3.8 (−4.4, −3.2)	<.001	2.1 (1.9)	−3.3 (−3.9, −2.8)	<.001
3 months	2.1 (1.9)	−3.5 (−4.1, −2.9)	<.001	2.3 (1.9)	−3.1 (−3.7, −2.6)	<.001
6 months	1.7 (1.7)	−3.8 (−4.4, −3.2)	<.001	1.7 (1.5)	−3.5 (−4.0, −2.9)	<.001

TABLE 5 (Continued)

Outcome variable	PBO (*N* = 51) mean (*SD*)	Mean difference (95% CI)	*p* value	DCS (*N* = 49) mean (*SD*)	Mean difference (95% CI)	*p* value
Target compulsions rating—parent						
Pretreatment	5.9 (1.3)	Ref.	Ref.	5.2 (1.5)	Ref.	Ref.
Posttreatment	2.6 (1.8)	−3.3 (−3.8, −2.8)	<.001	3.3 (1.9)	−2.0 (−2.5, −1.5)	<.001
1 month	2.3 (2.1)	−3.7 (−4.2, −3.2)	<.001	2 (1.6)	−3.2 (−3.8, −2.7)	<.001
3 months	1.9 (1.8)	−3.9 (−4.5, −3.4)	<.001	2.1 (1.8)	−3.1 (−3.7, −2.6)	<.001
6 months	1.9 (2.3)	−3.9 (−4.4, −3.3)	<.001	1.6 (1.8)	−3.6 (−4.1, 3.0)	<.001
Child OCD impairment—parent (COIS-P)						
Pretreatment	49.3 (29.3)	Ref.	Ref.	39.2 (26.5)	Ref.	Ref.
1 month	24.7 (23.9)	−23.8 (−31.2, −16.3)	<.001	19.2 (21.6)	−19.7 (−27.2, −12.3)	<.001

Note: Summary statistics presented as mean (standard deviation). Within-treatment differences presented as mean difference (95% confidence interval).
Abbreviations: CI, confidence interval; DCS, D-cycloserine.

TABLE 6 Clinical response and remission rates across time and treatment condition

	Placebo						DCS					
	Responder % (*n*)			Remitter % (*n*)			Responder % (*n*)			Remitter % (*n*)		
	Overall	No SSRI	SSRI	Overall	No SSRI	SSRI	Overall	No SSRI	SSRI	Overall	No SSRI	SSRI
T2	58.1 (25)	53.8 (14)	64.7 (11)	27.9 (12)	23.1 (6)	35.3 (6)	46.8 (22)	48.4 (15)	43.8 (7)	21.3 (10)	29.0 (9)	6.3 (1)
T3	71.8 (28)	81.8 (18)	58.8 (10)	51.3 (20)	54.5 (12)	47.1 (8)	64.3 (27)	75.0 (21)	42.9 (6)**	40.5 (17)	53.6 (15)	14.3(2)***
T4	70.0 (28)	70.8 (17)	68.8 (11)	45.0 (18)	54.2 (13)	31.3 (5)	57.1 (24)	60.7 (17)	50.0 (7)	42.3 (18)	46.4 (13)	35.7 (5)
T5	74.3 (26)	81.0 (17)	64.3 (9)	51.4 (18)	57.1 (12)	42.9 (6)	69.2 (27)	84.0 (21)	42.9 (6)***	48.7 (19)	60.0 (15)	28.6 (4)*

Note: Treatment response was defined by a reduction of 35% or greater on CY-BOCS severity, whereas remission was defined by CY-BOCS of 12 or less.
Significance: *$p < .06$, **$p < .05$, ***$p < .01$.
Abbreviations: DCS, D-cycloserine; ERP, exposure and response-prevention.

responders is warranted. Finally, further study of predictors and moderators of intensive ERP outcomes are warranted.

This RCT included evidence-based diagnostic and symptom severity assessments for a large sample of youth with OCD. Raters and therapists were trained to reliability, and closely supervised to ensure measurement reliability and treatment fidelity. We did not perform checks of blindness from children (or therapists), thus patient expectancy biases cannot be ruled out. Further, we did not obtain standardised assessments of subjective units of distress (SUDs) ratings within ERP sessions, and therefore could not examine the quality of within-session ERP (as marked by a decline in SUDs) as a possible moderator of outcome. Finally, we did not achieve the full a prior sample size due to failure to recruit to target and data loss across the trial, thus analyses of the overall sample were under-powered, and sub-group analyses more so. Based on the large individual patient data meta-analysis of Mataix-Cols et al., (2017), the overall effect size for DCS was found to be small ($d = 0.25$), requiring much larger samples to detect augmenting effects of DCS.

Overall, the current study did not find evidence for significant DCS augmentation of intensive ERP for paediatric OCD. There was no evidence for moderating effects of antidepressant use or child age on primary outcomes. The findings provide strong evidence for the effectiveness of intensive ERP in reducing child OCD diagnoses, symptoms, and impairment at posttreatment and 6-month follow-up but suggest that more research on augmentation strategies is required given that ERP for OCD, delivered in various formats, still leaves approximately 30% of children and adolescents with clinically significant symptoms and impairment.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Study concept and design: Lara J. Farrell, Jennifer L. Hudson, Ronald M. Rapee, Thomas H. Ollendick, Allison M. Waters, Melanie J. Zimmer-Gembeck, and Eric A. Storch. *Acquisition, analysis and/or interpretation of the data*: Lara J. Farrell, Robert S. Ware, Sharna Mathieu, Matthew McKenzie, Jacinda Cadman, and Cassie Lavell. *Drafting of the manuscript*: Lara J. Farrell, Robert S. Ware, Sharna Mathieu, and Melanie J. Zimmer-Gembeck. *Critical Revision of the Manuscript*: All authors. *Obtained funding*: Lara J. Farrell, Allison M. Waters, Eric A. Storch, Brett McDermott, Harry McConnell, Jennifer L. Hudson, Daniel Geller, Thomas H. Ollendick, Melanie J. Zimmer-Gembeck, and Evelin Tiralongo. *Administrative, technical, or material support*: Lara J. Farrell, Sharna Mathieu, Matthew McKenzie, Cassie Lavell, Jacinda Cadman, Vinay Garbharran, and Evelin Tiralongo. *Study Supervision*: Lara J. Farrell, Jennifer L. Hudson, Allison M. Waters, Evelin Tiralongo, Vinay Garbharran, Harry McConnell, and Jacinda Cadman. *Had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis*: Lara J. Farrell and Robert S. Ware.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Lara J. Farrell http://orcid.org/0000-0002-4231-2227

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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