

## Short report

# Cognitive–behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive–compulsive disorder: pilot randomised controlled trial

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## Summary

A partial *N*-methyl-D-aspartate agonist, D-cycloserine, enhances fear extinction when given before or shortly after exposure to feared stimuli in animals. In this pilot double-blind placebo-controlled trial (trial number: ISRCTN70977225), 27 youth with obsessive–compulsive disorder were randomised to either 50 mg D-cycloserine or placebo administered immediately after each of ten cognitive–behavioural therapy (CBT) sessions, primarily consisting of exposure and ritual prevention.

Both groups improved significantly and maintained their gains at 1-year follow-up, with no significant advantage of D-cycloserine over placebo at any time point. The effects of CBT may not be augmented or accelerated when D-cycloserine is administered after sessions.

## Declaration of interest

None.

The glutamatergic *N*-methyl-D-aspartate (NMDA) receptor is critically involved in learning and memory. A partial NMDA agonist, D-cycloserine, facilitates fear extinction and reduces return of fear when given before or shortly after exposure to feared stimuli in animals.<sup>1</sup> Several studies in anxiety disorders, including obsessive–compulsive disorder (OCD), have suggested that administration of D-cycloserine immediately before exposure therapy may augment or accelerate improvement.<sup>2–5</sup> Animal studies show that D-cycloserine facilitates fear extinction even if administered after exposure.<sup>3</sup> To date, all existing human trials but one<sup>6</sup> have administered D-cycloserine before exposure sessions. Because it is difficult to predict whether exposure will be successful before the session starts, administering D-cycloserine after sessions in which *in vivo* exposure actually took place, rather than before, makes intuitive sense. This pilot double-blind placebo-controlled trial (trial number: ISRCTN70977225) tested whether D-cycloserine augments and/or accelerates the effects of cognitive–behavioural therapy (CBT) for OCD when administered after CBT sessions incorporating *in vivo* exposure and ritual prevention (ERP). We expected a significant advantage of D-cycloserine at mid-treatment.<sup>4</sup>

## Method

Twenty-seven youth with a principal diagnosis of OCD were recruited from the OCD Clinic for Young People at the Maudsley Hospital, London (online Fig. DS1). Inclusion criteria were a confirmed diagnosis of OCD; Children's Yale–Brown Obsessive–Compulsive Scale (CY-BOCS)<sup>7</sup> score >16; stable on any psychotropic medications for ≥12 weeks; no comorbid psychosis, bipolar disorder, autism or substance misuse/dependence. Participant characteristics are shown in online Table DS1. Power calculations were based on an adult OCD trial,<sup>4</sup> which reported a maximum therapeutic effect of D-cycloserine over placebo at mid-treatment. We estimated that to obtain a statistically significant treatment effect on the CY-BOCS at alpha ( $\alpha$ )=0.05 and 80% power, we would require 12 patients in each group. Therefore we aimed to randomise a total of 24 patients. The protocol

allowed replacing individuals who dropped out of treatment, hence the final 27 participants.

After obtaining written consent/assent, participants and their parents completed the Anxiety Disorders Interview Schedule for DSM-IV,<sup>8</sup> the CY-BOCS (primary outcome measure) and secondary measures. The CY-BOCS was readministered following an 8-week wait period to ensure that only participants who remained symptomatic were included. Following this, participants were randomly allocated via an external computer allocation system to receive either 50 mg D-cycloserine or placebo in a double-blind design. The D-cycloserine and identical placebo capsules were manufactured for the study at Guy's and St Thomas's Hospital production pharmacy (London, UK), in accordance with Good Manufacturing Practice.

The 14-session manualised treatment was delivered by experienced therapists and incorporated psychoeducation (two sessions), ERP (ten sessions) and relapse prevention (two sessions) delivered over a 17-week period. The protocol required that sessions 3–12 included *in vivo* ERP. Immediately after each of these ten ERP sessions, a psychiatrist administered one dose of either D-cycloserine or placebo. Homework ERP tasks were set each week and reviewed in the next session. Homework adherence was monitored using the Patient ERP Adherence Scale (PEAS).<sup>9</sup> Adverse effects were carefully monitored by telephone the day following each session using the Safety Monitoring Uniform Report Form.<sup>10</sup> A masked rater administered the CY-BOCS at the beginning of each session, providing session-by-session data. Double-blind follow-up assessments were completed at 3, 6 and 12 months post-treatment. Unmasking took place after the last patient had completed the 12-month follow-up.

General linear mixed models for group means as fixed effects, while simultaneously modelling for individual participant variables as random effects, were implemented in Stata (version 11 for Windows). This approach is superior to traditional repeated measures analyses of variance in handling missing data points while modelling the influence of non-linear individual differences across time.<sup>11</sup> Logistic regressions demonstrated that no baseline variables predicted missingness of data at any time point; hence, any missing data were treated as 'missing at random'.

## Results

On intention-to-treat (ITT) analyses, both groups improved significantly and robustly over time on the CY-BOCS (regression coefficient  $-3.80$ , 95% CI  $-4.76$  to  $-2.83$ ,  $z$ -score  $-7.74$ ,  $P < 0.001$ ). There were no statistically significant group (coefficient  $0.41$ , 95% CI  $-3.08$  to  $3.90$ ,  $z$ -score  $0.23$ ,  $P = 0.82$ .) or group  $\times$  time interaction (coefficient  $0.36$ , 95% CI  $-1.04$  to  $1.75$ ,  $z$ -score  $0.50$ ,  $P = 0.614$ ) effects on the CY-BOCS; the expected early augmentation effects were not observed (online Fig. DS2, online Table DS2). Treatment response (defined as  $\geq 35\%$  reduction on the CY-BOCS) was seen in 8 D-cycloserine and 9 placebo patients at post-treatment and 9 D-cycloserine and 12 placebo patients at 12-month follow-up. Remission (defined as CY-BOCS scores  $\leq 10$ ) was seen in 7 D-cycloserine and 6 placebo patients at post-treatment and 9 D-cycloserine and 10 placebo patients at 12-month follow-up.

Both groups improved significantly on all secondary measures, including self- and parent-reported OCD symptoms, depression and global functioning (Table DS2). There were no significant group (all  $P > 0.05$ ) or group  $\times$  time interaction (all  $P > 0.05$ ) effects on any secondary measures. No participant reported adverse drug reactions attributable to D-cycloserine or placebo.

## Discussion

To our knowledge, this is the first study to test whether D-cycloserine administered after ERP sessions enhances the effects of CBT in OCD. It is also the first to evaluate the long-term (12-month) effects of D-cycloserine *v.* placebo in an anxiety disorder. Administration of D-cycloserine after ten CBT sessions incorporating ERP did not augment or accelerate the process of recovery either acutely or in the long term. The results echo those of a similar study in acrophobia.<sup>6</sup> Previous research has suggested that the augmenting effects of D-cycloserine may be particularly evident early in treatment and that differences between D-cycloserine and placebo decrease over time.<sup>12</sup> In fact, none of the previous D-cycloserine studies in OCD reported significant augmentation at post-treatment. Session-by-session analyses of our data found no evidence of superiority of D-cycloserine over placebo at any time point.

Previous animal work has shown that D-cycloserine has its biggest effects in augmenting fear extinction if administered immediately before or after exposure, and NMDA-dependent fear extinction is thought to continue 1–2 days after training.<sup>3</sup> It is therefore likely that post-exposure administration of D-cycloserine reaches the salient site of action in a time course necessary to obtain an effect, but it remains a possibility that this timing of the dose of D-cycloserine is ineffective in humans.<sup>6</sup> However, other explanations are possible. First, the trial may have been underpowered and the results should be considered preliminary. However, earlier similar sized trials did find a modest advantage of D-cycloserine over placebo in OCD<sup>4</sup> and other anxiety disorders.<sup>2,3</sup> Furthermore, like previous negative trials,<sup>13</sup> our study involved a full course of CBT and very experienced therapists, thus potentially allowing less room for D-cycloserine to show superiority over placebo. If this were the case, D-cycloserine may be particularly useful in clinical settings where experienced therapists are not available or where funding is provided for only a small number of sessions. Third, we chose a dose of 50 mg, which had been effective in previous anxiety disorder trials (e.g. Ressler *et al.*<sup>2</sup>), but it is currently unclear to what extent the dose may moderate treatment efficacy.<sup>3</sup> Of note, the previous OCD trials with positive findings<sup>3,4</sup> employed larger D-cycloserine doses (100–125 mg).

Clearly more research is required to fully understand the clinical effects of D-cycloserine in human anxiety disorders. From this study, we conclude that CBT incorporating ERP is an effective and powerful treatment on its own and that administration of D-cycloserine after sessions may not augment or accelerate its effects. However, given the limited statistical power, the conditions under which D-cycloserine accelerates the clinical response to exposure-based treatments warrant the continuation of translational research.

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## References

- Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry* 2006; **60**: 369–75.
- Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, et al. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Arch Gen Psychiatry* 2004; **61**: 1136–44.
- Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biol Psychiatry* 2008; **63**: 1118–26.
- Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearson GD, Reese HE, et al. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165**: 335–41.
- Storch EA, Murphy TK, Goodman WK, Geffken GR, Lewin AB, Henin A, et al. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biol Psychiatry* 2010; **68**: 1073–6.
- Tart CD, Handelsman PR, Deboer LB, Rosenfield D, Pollack MH, Hofmann SG, et al. Augmentation of exposure therapy with post-session administration of D-cycloserine. *J Psychiatr Res* 2013; **47**: 168–74.
- Scahill L, Riddle MA, McSwiggan-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive-Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 844–52.
- Silverman WK, Albano AM. *Anxiety Disorders Interview Schedule for Children – IV, Child and Parent Versions*. Psychological Corporation, 1996.
- Simpson HB, Maher M, Page JR, Gibbons CJ, Franklin ME, Foa EB. Development of a patient adherence scale for exposure and response prevention therapy. *Behav Ther* 2010; **41**: 30–7.
- Greenhill LL, Vitiello B, Fisher P, Levine J, Davies M, Abikoff H, et al. Comparison of increasingly detailed elicitation methods for the assessment of adverse events in pediatric psychopharmacology. *J Am Acad Adolesc Psychiatry* 2004; **43**: 1488–96.
- Cnaan A, Laird N, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med* 1997; **16**: 2349–80.
- Chasson GS, Buhlmann U, Tolin DF, Rao SR, Reese HE, Rowley T, et al. Need for speed: evaluating slopes of OCD recovery in behavior therapy enhanced with D-cycloserine. *Behav Res Ther* 2010; **48**: 675–9.
- Storch EA, Merlo LJ, Bengtson M, Murphy TK, Lewis MH, Yang MC, et al. D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2007; **22**: 230–7.

