



Original article

D-cycloserine addition to exposure sessions in the treatment of patients with obsessive-compulsive disorder

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ABSTRACT

Background: Preliminary studies have shown that the addition of the partial NMDA-agonist D-cycloserine (DCS) might be promising in enhancing the results of exposure therapy in obsessive-compulsive disorder (OCD). We examined the effect of DCS addition to exposure therapy in a somewhat larger sample of OCD patients with special attention to subgroups, because of the heterogeneity of OCD.

Methods: A randomized, double-blind, placebo controlled trial was conducted in 39 patients with OCD. Patients received 6 guided exposure sessions, once a week. One hour before each session 125 mg DCS or placebo was administered.

Results: Scores on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) declined more in the DCS group than in the placebo group, but the difference did not reach statistical significance ($P = 0.076$, partial $\eta^2 = 0.13$). Response percentages also did not differ between the DCS and the placebo group (37% and 15% respectively). In the 'cleaning/contamination' subgroup a significant effect was found in favour of DCS ($P = 0.033$, partial $\eta^2 = 0.297$).

Conclusions: The results of this study did not support the application of DCS to exposure therapy in OCD. Some specific aspects need further investigation: efficacy of DCS in a larger 'cleaning/contamination' (sub-)group, DCS addition only after successful sessions, interaction with antidepressants.

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1. Introduction

Evidence-based treatment options for obsessive-compulsive disorder (OCD) are pharmacological interventions, particularly with serotonin reuptake inhibitors [1,2] and cognitive behavior therapy (CBT) [3,4]. Despite the efficacy of these treatment options, the rate of non-response is still unsatisfactory and the mean decrease in symptoms mostly is moderate [5,6]. In clinical practice pharmacotherapy and CBT are often combined. Yet, the evidence that the addition of pharmacotherapy to CBT yields more effect than CBT alone is not very convincing [7,8].

This means there is a need for better and new approaches in the treatment of OCD in order to achieve a greater response and remission percentage. During the last years much research has been done on D-cycloserine and its use as an adjunctive psychopharmacological tool added to CBT treatment in anxiety disorders. D-cycloserine (DCS) acts as a partial N-methyl-D-aspartate

(NMDA) receptor agonist [9]. By stimulating the receptor at the glycine site it enhances extinction of conditioned fear. This has been established in animal models and in studies with anxiety disorder patients [10]. Exposure and response prevention (ERP), the key element of CBT in OCD [11], is the analogue of the procedure of extinction of conditioned fear in animals. In line with these findings the potential augmenting effect of DCS of CBT treatment in OCD has been examined in three studies with adult patients and three studies with adolescent patients. In two double-blind randomized placebo controlled studies [12,13] no statistically significant additional effect (as measured with the Yale-Brown Obsessive-Compulsive Scale; Y-BOCS) of DCS to the ERP treatment of OCD patients was found at the end of the treatment period (12, and up to 5 weeks respectively). However, in both studies measurements after the first sessions showed tendencies to a faster improvement when DCS was added. In a third publication concerning a randomized placebo controlled trial in adult OCD patients DCS augmented the effect of ERP; statistically significant only at mid-treatment, but a moderate to large Cohen's effect size at posttreatment [14]. In three preliminary studies in pediatric OCD patients no significant augmenting effects of DCS were found at posttreatment [15–17]. However, effect sizes were moderate in one

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study ($d = 0.31$ to 0.47) [15] and in another study [16] DCS addition did better at follow-up ($d = 0.5$). All together there are some indications that the addition of DCS to ERP treatment in OCD enhances improvement, which seems to be most apparent during the first sessions of the treatment [18]. Due to the preliminary aspect of these studies all have limitations, such as limited numbers of participants (around 25 subjects), heterogenic patient groups, varying doses of DCS (100, 125 and 250 mg used), times of administration (1, 2 and 4 hours before, or directly after treatment sessions) and ERP schedules (weekly or twice weekly).

In order to examine further the potential augmenting effect of DCS to ERP in OCD patients using a somewhat larger sample we designed the present study. We included OCD patients and used a limited series of ERP sessions delivered weekly, as is usual in ambulatory CBT treatment. We chose to use a dose of 125 mg DCS, administered 1 hour before ERP sessions.

We hypothesized that administration of DCS as an adjunctive to ERP treatment in OCD will enhance improvement after six sessions of ERP when compared to placebo addition. OCD is a heterogeneous disorder and it is known that different symptom dimensions, symptom severity and schizotypal symptoms can influence the responsiveness to CBT and possibly to the additional effect of DCS [19–21]. Therefore, we also planned to explore the effect of DCS addition in some defined subgroups.

2. Methods

2.1. Participants

A total of 51 patients were referred for the screening phase. See Fig. 1 for the flow-scheme. Patients were mainly recruited at the Marina de Wolf center, GGz Centraal, Ermelo, and an additional few at Overwaal, Lent, both anxiety disorders clinics in the Netherlands. The enrollment was from March 2009 till December 2011. The study was conducted according to the latest version of the Declaration of Helsinki. The study protocol was approved by the medical ethics review committee of the mental health institutes in the Netherlands (METiGG). All participants signed

an informed consent form. The trial was registered at trialregister.nl (NTR1189).

Included were patients with a primary DSM-IV diagnosis of OCD with an age of 18 years and older. Concurrent medication was permitted, except for benzodiazepines, but doses had to be stable for the last two months and during the trial period. Exclusion criteria were:

- substance addiction or abuse;
- primary diagnosis of a personality disorder;
- psychotic disorder (current or in the past);
- severe somatic disorders and disorders that may interfere with the behavior therapy;
- suicidal intentions;
- pregnancy or breastfeeding;
- usage of medication possibly interfering with DCS (isoniazide, protonionamide);
- currently undergoing psychotherapy;
- mental retardation and/or not understanding the rationale of exposure therapy.

Female patients were required to use a reliable contraceptive.

2.2. Procedure

Patients were referred to the clinic for the screening. They already had received global information about the study and were willing to participate. The screening procedure consisted of a psychiatric and medical investigation and confirmation of the diagnoses using the Structural Clinical Interview for axis I DSM-IV Disorders (SCID I) [22]. When patients were eligible they were randomized in a double-blind manner to the two treatment conditions: exposure and response prevention (ERP) plus D-cycloserine (DCS) or ERP and placebo. The randomization code was preserved at the clinical trials department of the pharmacy of the University Medical Center Utrecht, where the D-cycloserine and placebo capsules were manufactured and dispensed.

Patients then received 7 weekly treatment sessions. The first session consisted of psycho-education, explaining the rationale of

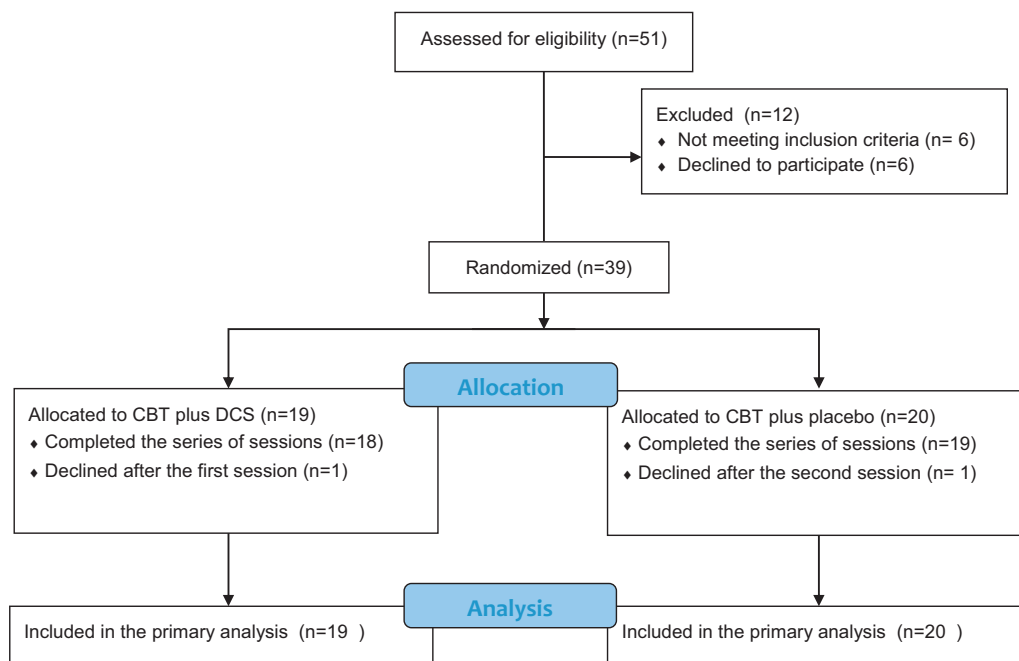


Fig. 1. Patient flow diagram.

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