A Randomized Placebo-Controlled Trial of D-Cycloserine to Enhance Exposure Therapy for Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is a complex and debilitating anxiety disorder, and, although prolonged exposure therapy has been proven effective, many patients remain symptomatic after treatment. In other anxiety disorders, the supplementary use of D-cycloserine (DCS), a partial agonist at the glutamatergic *N*-methyl-D-aspartate receptor, showed promise in enhancing treatment effects. We examined whether augmentation of prolonged exposure therapy for PTSD with DCS enhances treatment efficacy.

Methods: In a randomized, double-blind, placebo-controlled trial we administered 50 mg DCS or placebo 1 hour before each exposure session to 67 mixed trauma patients, recruited from regular referrals, with a primary PTSD diagnosis satisfying DSM-IV criteria.

Results: Although DCS did not enhance overall treatment effects, the participants having received DCS did show a stronger treatment response. Exploratory session-by-session analyses revealed that DCS yielded higher symptom reduction in those participants that had more severe pretreatment PTSD and needed longer treatment.

Conclusions: The present study found preliminary support for the augmentation of exposure therapy with DCS, specifically for patients with more severe PTSD needing longer treatment.

Key Words: Cognitive behavioral therapy, cognitive enhancers, D-cycloserine, posttraumatic stress disorder, prolonged exposure, treatment efficacy

Posttraumatic stress disorder (PTSD) is an anxiety disorder with a lifetime prevalence of approximately 8% (1,2). PTSD is often accompanied by comorbid psychiatric disorders (1), and sufferers are frequently impaired in daily life and work functioning. There are various effective treatment strategies available. Several controlled studies demonstrated the efficacy and effectiveness of prolonged exposure therapy (PE), a cognitive behavioral therapy for the treatment of PTSD (for overview see Powers *et al*. [3]). Consequently, PE is considered a first-line treatment for PTSD (4,5). In PE, patients are asked to vividly recount the traumatic experience and to confront fear-evoking trauma-related stimuli (6). The proposed working mechanism of PE is fear extinction by effective emotional processing of the traumatic memory. Notwithstanding the efficacy of PE, improvements are needed, given that many patients remain symptomatic after treatment (7,8). With studies reporting rates of 20% to 35%, dropout is also an important issue (9–11).

To improve treatment efficacy in anxiety disorders, researchers are focusing on the pharmacologic enhancement of the mechanisms of extinction-based (exposure) therapies. Fear extinction has been linked to *N*-methyl-D-aspartate (NMDA) glutamatergic receptor activity in the basolateral amygdala (12). Animal research suggested that NMDA receptor agonists, such as the partial agonist D-cycloserine (DCS), can enhance extinction effects (13,14). Clinical studies that subsequently examined whether fear extinction is indeed facilitated by supplementing exposure therapy with DCS found augmentation effects in patients with specific phobia (15), social phobia (16,17), panic disorder (18,19) and obsessive-compulsive disorder (20–22). Although the findings of some studies were less pronounced (e.g., Siegmund *et al*. [19] and Wilhelm *et al*. [20], respectively, found enhancement effects for severely disordered patients and at midtreatment only), overall, DCS showed promise in augmenting exposure-based therapy (for a review, see Norberg *et al*. [12]). Findings in studies using a single prolonged stress paradigm in rats as an animal model of PTSD (23,24) suggested that DCS might also be effective in the treatment of this disorder, but to our knowledge the exposure-enhancing properties of DCS have to date not been systematically investigated in this population.

One pilot study did test DCS in PTSD patients but as a stand-alone therapy, that is, without additional exposure or other emotional learning treatment techniques (25), despite the general assumption that DCS as such does not positively influence treatment outcome, but does so solely by augmentation of exposure effects. The trial was also limited in that it included only 11 patients. Moreover, DCS was administered on a daily basis, whereas chronic use, as opposed to acute use for the facilitation of exposure sessions, is known to lead to negative effects (13,15). It was therefore not surprising that no beneficial effects were found.

In conclusion, in patients with anxiety disorders, augmenting exposure-based therapies with DCS appears promising in improving treatment outcome, but controlled PTSD studies are lacking. With the present study, we aimed to test the efficacy of DCS in combination with PE for PTSD in a randomized, double-blind, placebo-controlled design. We hypothesized that the patients receiving DCS would profit more from PE than those receiving placebo. In addition, we explored the effects of DCS over the course of the treatment by analyzing weekly changes in PTSD symptoms.

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Table 1. Sample Characteristics

Characteristic	D-Cycloserine[a]	Placebo[a]	*p* Value (Two-Sided)
Sample Size	33	34	NA
Age, Mean (SD) in Years	36.27 (11.56)	40.26 (11.05)	.15[b]
Female	29 (87.9)	25 (73.5)	.14[c]
Married or Cohabitating	11 (33.3)	14 (41.2)	.51[c]
Post–High School Education	23 (69.7)	23 (67.6)	.86[c]
Trauma History			.42[c]
Sexual assault	14 (42.2)	21 (61.8)	
Violent nonsexual assault	12 (36.4)	8 (23.5)	
Accident	1 (3.0)	2 (5.9)	
War-zone experiences	1 (3.0)	1 (2.9)	
Miscellaneous	5 (15.2)	2 (5.9)	
Axis I Comorbidity (Current)	22 (66.7)	25 (73.5)	.54[c]
Comorbid Anxiety Disorder	14 (42.4)	14 (41.2)	.92[c]
Comorbid Depressive Disorder	15 (45.5)	21 (61.8)	.18[c]
Receiving Psychotropic Medication	13 (39.4)	15 (44.1)	.70[c]

NA, not applicable.
[a]Values are expressed as numbers (percentages) unless otherwise indicated.
[b]Value obtained by *t* test.
[c]Values obtained by χ^2 test.

Methods and Materials

Participants

All participants were regular referrals to two Dutch outpatient clinics specializing in the treatment of anxiety disorders. Participants were enrolled between March 2008 and March 2010, with final follow-ups completed in June 2010. After regular pretreatment screening, a member of the research team invited eligible patients to participate in the study. Inclusion criteria were 1) age between 18 and 65 years and 2) current PTSD DSM-IV diagnosis (26) confirmed by a structured diagnostic interview (see Measures). Exclusion criteria were 1) (current or past) psychosis or delusional disorders, 2) acute suicidal tendency, 3) mental retardation, 4) substance abuse or dependence, 5) pregnancy or lactation, 6) a serious and unstable medical condition (e.g., pacemaker, renal disease, porphyria), 7) a history of epileptic seizures, 8) medication use that might interfere with DCS (e.g., anticoagulants), 9) insufficient ability to speak and write Dutch. Written informed consent was obtained from all volunteer participants. The study protocol was approved by the medical ethics committee of the Radboud University Nijmegen Medical Centre.

Of the 75 eligible participants[1] randomly assigned in double-blind fashion to the treatment conditions, 8 dropped out before the first exposure session, leaving 67 participants receiving the allocated intervention. The treatment protocol was completed by 45 participants, 24 receiving exposure plus DCS and 21 receiving exposure plus placebo, whereas 40 completers and 5 dropouts completed the 3-month follow-up assessment. No significant differences between completers and dropouts were found for any sample characteristic or baseline symptom severity measures.

The sample characteristics are presented in Table 1. The majority of the patients (80.6%) were female, and the sample's mean age was 38.3 (SD = 11.4) years. The traumatic events underlying PTSD were mixed and comprised sexual assault including childhood sexual abuse ($n = 35$), violent nonsexual assault ($n = 20$), a road traffic or other accident ($n = 3$), war-zone experiences ($n = 2$), and miscellaneous ($n = 7$). Less than half of the participants (41.8%), who were equally distributed across the two groups, were taking psychotropic medication: 11 a benzodiazepine, 8 an antidepressant, and 9 both benzodiazepines and antidepressants. All had been on a stable dose before allocation and agreed to maintain the regular dose throughout the trial. All participants met the DSM-IV criteria for PTSD, and diagnostic interviews (Mini-International Neuropsychiatric Interview [M.I.N.I.]) (27) revealed that 70.1% ($n = 47$) had at least one additional diagnosis (mean 2.0). The most common Axis I disorders were depressive disorder (53.7%) and anxiety disorders (41.8%).

No significant group differences were found for gender, age, education, trauma type, comorbidity, and psychotropic medication use.

Measures

The DSM-IV Axis I diagnoses of PTSD and any comorbid conditions were established with the M.I.N.I. (27), a valid and reliable structured interview to assess Axis I psychiatric diagnoses.

The primary outcome measure was PTSD symptom severity as assessed with the Clinician-Administered PTSD Scale (CAPS-1) (28), a clinician-rated structured interview developed to test for the presence of the 17 DSM-IV-TR criteria for PTSD. The interrater diagnostic agreement was shown to be excellent (29), as was the internal consistency ($\alpha = .94$) (28), and the concurrent validity was adequate (28,29). Symptoms of PTSD were also assessed with the Posttraumatic Stress Symptom Scale—Self Report (PSS-SR) (30), a 17-item questionnaire with which patients rate the frequency of PTSD symptoms. Analyses showed a high internal consistency (Cronbach's alpha = .91) (30). The Dutch version also shows good internal consistency (31).

As secondary measures, we assessed general anxiety, depression and general psychopathology. General anxiety was evaluated with the state subscale of the State and Trait Anxiety Inventory (32,33); the state portion of the inventory comprises 20 items regarding state anxiety and gauges the level of anxiety the respondent experiences at the time of assessment. The internal consistency of the Dutch version is between .86 and .95 (33). Depression was assessed using the Beck Depression Inventory (34), a 21-item self-report questionnaire measuring the severity of depressive

[1]For administrative reasons, participants were randomized before the baseline assessments. Consequently, 16 patients received a randomization number but never entered the study because they were excluded or withdrew before completion of the baseline assessment.