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Extinction learning as a moderator of D-cycloserine efficacy for enhancing exposure therapy in posttraumatic stress disorder

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ABSTRACT

Augmentation of exposure therapy with D-cycloserine (DCS) has proven efficacious across anxiety disorders, although results in PTSD have been mixed. Work in animals and anxiety-disordered patients suggest that the potentiating effects of DCS are dependent on the level of extinction learning during extinction training and exposure treatment, respectively. The aim of the current study was to replicate and extend previous work by examining the association between the degree of extinction learning and DCS efficacy in our randomized clinical trial on DCS (50 mg) versus placebo enhancement of exposure therapy in a chronic mixed-trauma PTSD sample ($N = 67$; de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012). The decline in subjective units of distress ratings collected during and across the exposure sessions were evaluated as indices of extinction learning. First, we examined whether extinction learning during an exposure session moderated DCS effects on self-reported PTSD symptoms at the next session. Second, we examined whether averaged extinction learning over the course of treatment interacted with group assignment to predict change over time and post treatment outcome. We did not find evidence that DCS effects were moderated by the degree of extinction learning, although, extinction learning was related to outcome regardless of group assignment. In PTSD, not one extinction-learning index has been consistently linked to DCS enhanced exposure treatment outcome. More (experimental) work needs to been done to unravel the complex interplay between extinction learning and DCS enhancement, especially in PTSD patients.

1. Introduction

D-cycloserine (DCS), a partial agonist of the NMDA receptor, has been tested as an augmentation strategy for exposure therapy effects because it is thought to enhance the consolidation of extinction learning (Davis, Ressler, Rothbaum, & Richardson, 2006), a key mechanism of action of exposure therapy. Accumulating evidence points to the efficacy of this novel augmentation strategy (see for meta-analyses: Bontempo, Panza, & Bloch, 2012; Norberg, Krystal, & Tolin, 2008; Rodrigues et al., 2014), but results of these clinical studies have been mixed, especially in the treatment of posttraumatic stress disorder (PTSD). Difede et al. (2014), who investigated DCS enhanced virtual reality exposure therapy (VRET) for civilian PTSD patients following the WTC-attacks, showed faster and greater symptom decline for those who received DCS. de Kleine et al. (2012) investigated the DCS enhancement effects of prolonged exposure (PE) in a civilian chronic, mixed-trauma sample, and observed no overall improvement in outcome, although DCS did augment effects in a subgroup of more severe patients that needed longer treatment. Similarly, Rothbaum et al. (2014) failed to find overall enhancement effects of DCS compared to placebo and alprazolam in a large veteran population using VRET, but did show that DCS reduced physiological reactivity to trauma relevant cues. In a mixed trauma sample of 7–18 year-old youth, Scheeringa and Weems (2014) found no evidence of DCS facilitation using a cognitive behavioral therapy program, including exposure exercises. Importantly, Litz et al. (2012) actually observed negative effects for DCS augmentation of exposure treatment albeit in a small veteran PTSD sample.

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There are a number of possible explanations for the observed inconsistencies across studies. First, it has been put forward that methodological differences across studies could account for the different outcomes (Hofmann, Smits, Asnaani, Gutner, & Otto, 2011). For instance, dose, timing and number of DCS administrations have differed among studies. Second, it has been suggested that person-level variables, such as symptom severity (Guastella, Dadds, Lovibond, Mitchell, & Richardson, 2007; Siegmund et al., 2011), antidepressant use (Werner-Seidler & Richardson, 2007) or personality traits could influence DCS effects. In support, de Kleine, Hendriks, Smits, Broekman, and van Minnen (2014) found that personality traits (conscientiousness and extraversion) influenced DCS effects in PTSD patients. Third, in line with the proposed working mechanism of DCS, it has been stipulated that enhancement effects may be influenced by the amount of (extinction) learning during treatment (for instance Litz et al., 2012). Indeed, in preclinical paradigms it has been found that DCS was especially beneficial for animals that showed more within-session extinction during training (Bolkan & Lattal, 2014; Bouton, Vurbic, & Woods, 2008; Weber, Hart, & Richardson, 2007). When the amount of extinction learning during training was experimentally restricted, DCS was found to have no augmentation (Bouton et al., 2008) or even detrimental effects (Lee, Milton, & Everitt, 2006). This suggests that when there is not sufficient extinction learning, DCS might potentiate reconsolidation of the fear memory, which has been translated clinically into "DCS might make a good exposure better, and a bad exposure worse" (Litz et al., 2012, p. 1189).

Recent reanalyses of clinical trial data on DCS enhanced exposure treatment support this hypothesis. Smits, Rosenfield, Otto, Marques, et al. (2013a); Smits, Rosenfield, Otto, Powers, et al. (2013b) found that the fear levels at the end of an exposure session interacted with DCS effects in their trial on DCS enhanced virtual reality treatment in acrophobic patients. That is, compared to placebo, those who received DCS and had low fear at the end of the exposure session improved *more* in the following week, while those with relatively high end fear improved *less*. A similar pattern was found in a large social phobic sample. In addition to the per session effects, DCS enhancement effects at post treatment were only evident among those who had low end fear during the sessions that were augmented with DCS (Smits, Rosenfield, Otto, Marques, et al., 2013a). In this latter study, Smits and colleagues examined additional indices of extinction learning, namely peak fear levels and decrement of fear within-session (i.e., peak fear minus end fear), but found the strongest moderating effects for end fear.

Whether extinction learning moderates DCS efficacy for enhancing PE for PTSD is unclear. Litz et al. (2012) found less within-session extinction in some (but not all) exposure sessions for those receiving DCS compared to placebo, and suggested that these differences were related to their negative outcome for DCS, but did not report on the test of this hypothesized effect. Rothbaum et al. (2014) found that DCS enhancement effects were stronger among patients who showed greater between-session extinction learning over the course of treatment, but did not report on the moderator effects of end fear or within-session extinction.

To conclude, the aim of the present study is to further investigate whether DCS enhancement effects are moderated by the degree of extinction learning during exposure therapy in PTSD. Specifically, we hypothesize that DCS enhancement effects are specific to sessions that are successful or associated with low end fear levels. Extinction learning consolidation is thought to occur hours after the end of exposure sessions, and when DCS is administered just before or immediately after exposure sessions, peak blood levels of DCS overlap with this consolidation window. Accordingly, if we observed the expected moderation effect in our study, our findings would suggest that learning process are indeed underlying DCS efficacy, and imply that clinicians should be judicious in applying DCS in conjunction with PE.

2. Materials and methods

This study is a reanalysis of clinical trial data on DCS enhancement of PE in PTSD (trial registration: www.trialregister.nl, NTR1184). For a full description of the trial methods and materials we refer to the parent trial (de Kleine et al., 2012).

2.1. Participants

Sixty-seven participants were recruited in two Dutch regular mental health care facilities. The sample consisted predominantly of women (88%), and trauma-type was mixed, with most of the participants being survivors of sexual violence, including childhood sexual abuse. Participants who fulfilled any of the following criteria were excluded: (1) (current or past) psychosis or delusional disorders, (2) current suicidal intent, (3) mental retardation, (4) satisfying DSM-IV criteria for substance abuse or dependence, (4) pregnancy or lactation, (5) a serious and unstable medical condition (e.g., pacemaker, renal disease or porphyria), (6) a history of epileptic seizures, (7) medication use that might interfere with DCS (e.g., anticoagulants), (8) insufficient ability to speak and write Dutch. Co-morbidity rates were high, with over 70% suffering from at least one comorbid Axis I disorder. During treatment, 22 participants (33%) dropped out prematurely, leaving 45 treatment completers. The drop-out rate between groups did not differ significantly (DCS: $N = 9$ (27%); Placebo: $N = 13$ (38%); $\chi^2_1 = 0.913$, $p = .339$).

2.2. Treatment

All participants received manualized PE treatment (see Foa, Hembree, & Rothbaum, 2007), with a maximum of 10 sessions. In the first session, participants received psychoeducation on PTSD symptoms and the treatment rationale. Based on the prior work by van Minnen and Foa (2006), the subsequent weekly exposure sessions comprised 30 min of imaginal exposure (rather than the 45–60 min of the original PE protocol). Patients were instructed to imagine the traumatic event as vividly as possible and to repeatedly recount it aloud in the present. Throughout imaginal exposure, fear levels were monitored by subjective units of distress (SUD; Wolpe, 1958) ratings on a scale of 0 (no fear) to 100 (maximum fear). SUD ratings were obtained right before the start of imaginal exposure every 5 min, and immediately at the end of imaginal exposure. All therapists ($N = 25$) were psychologists trained in PE treatment for PTSD, and all weekly sessions were supervised. In a previous study (Hagenaars, van Minnen, & Hoogduin, 2010), we had found that a proportion of patients terminated treatment early, because they had reached (full) recovery. To allow for early termination, we defined stopping rules: if the PSS-SR score was below 15 on two subsequent sessions, and if there was patient-therapist agreement on improvement, patients could end treatment. The mean number of total sessions received was 7.22 (SD = 2.58).

2.3. Design

After enrollment, participants were randomly allocated in double blind fashion to receive prolonged exposure plus placebo (microcrystalline cellulose PH-102; $N = 33$) or prolonged exposure plus D-cycloserine (50 mg; $N = 34$). Study drugs (identical in appearance) were dispensed by an independent pharmacist in numbered containers in accordance with a computer generalized randomization list. Participants ingested the study drug 60 min prior to each prolonged exposure session. The study protocol was approved by the medical ethics committee of the Radboud University Nijmegen